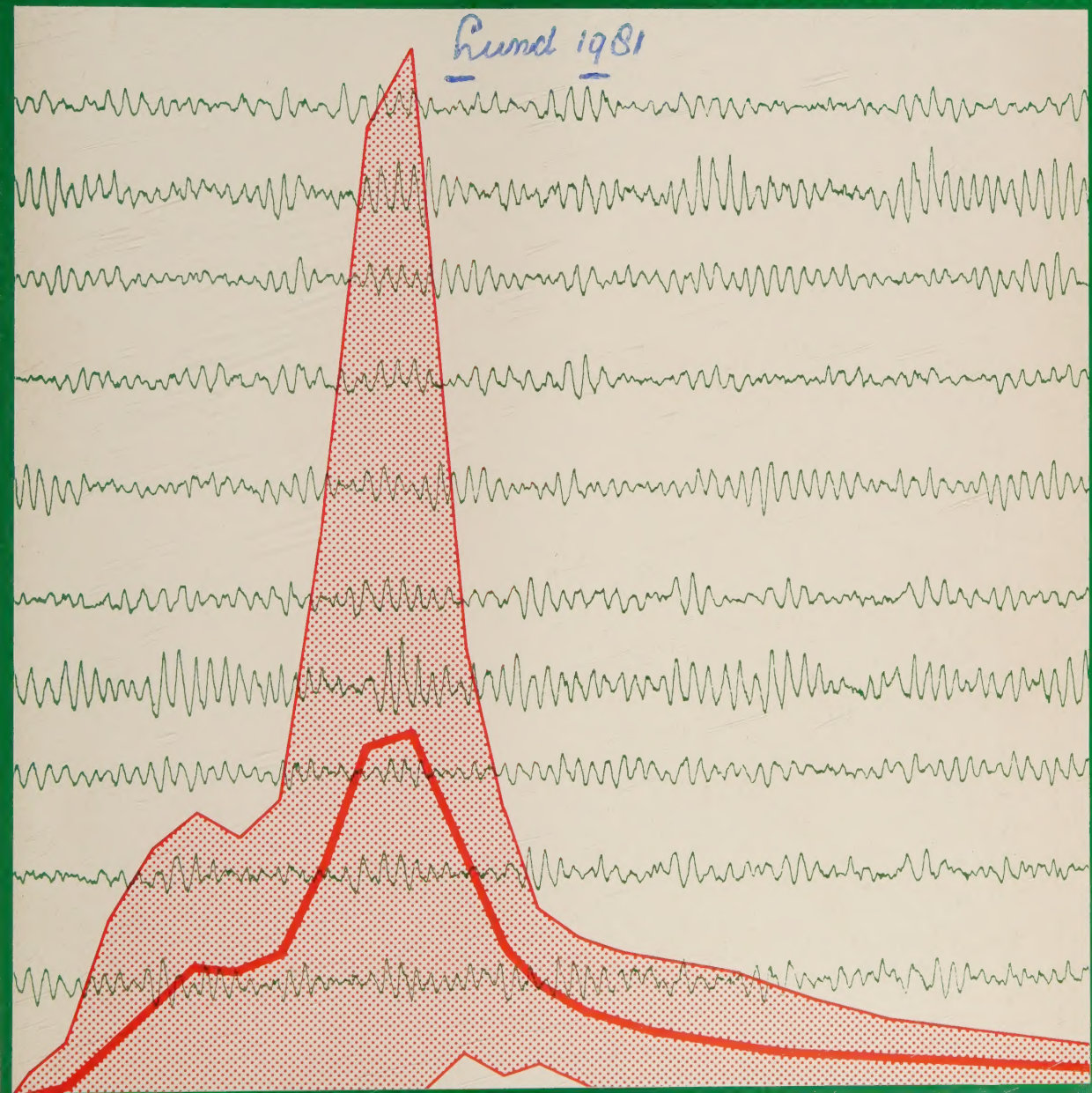


BENT STIGSBY: PERIOD-AMPLITUDE ANALYSIS OF THE ELECTROENCEPHALOGRAM

METHODOLOGY AND
CLINICAL
APPLICATIONS





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ANALYSIS OF THE
ELECTROENCEPHALOGRAM

W. K. UCHIDA AND
J. L. GILSON
MAY 1963

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CLINICAL
APPLICATIONS

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AKADEMISK AVHANDLING

Som för avläggande av doktorsexamen vid medicinska fakulteten
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To
Gunilla Stjernström Stigsby

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LIST OF PAPERS

- I. Stigsby, B., Obrist, W.D. and Sulg, I.A. Automatic data acquisition and period-amplitude analysis of the electroencephalogram. *Comput. Programs Biomed.*, 1973, 3: 93-104.
- II. Kardel, T., Zander Olsen, P., Stigsby, B. and Tønnesen, K. Hepatic encephalopathy evaluated by automatic period analysis of the electroencephalogram during lactulose treatment. *Acta Med. Scand.*, 1972, 192: 493-498.
- III. Kardel, T. and Stigsby, B. Period-amplitude analysis of the electroencephalogram correlated with liver function in patients with cirrhosis of the liver. *Electroencephalogr. Clin. Neurophysiol.*, 1975, 38: 605-609.
- IV. Stigsby, B., Risberg, J. and Ingvar, D. H. Electroencephalographic changes in the dominant hemisphere during memorizing and reasoning. *Electroencephalogr. Clin. Neurophysiol.*, 1977, 42: 665-675.
- V. Stigsby, B., Jóhannesson, G. and Ingvar, D.H. Regional EEG analysis and regional cerebral blood flow in Alzheimer's and Pick's disease. *Electroencephalogr. Clin. Neurophysiol.*, 1981, accepted for publication: January 22, 1981.
- VI. Stigsby, B., Rodenberg, J.C. and Moth, H.B. Electroencephalographic findings during mantra meditation (transcendental meditation). A controlled, quantitative study of experienced meditators. *Electroencephalogr. Clin. Neurophysiol.*, 1981, 51: 434-442.

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INTRODUCTION

Three years after the first publication on the human electroencephalogram (Berger 1929), Dietsch (1932) quantitated a small sample of EEGs by Fourier transformation, a tremendous task at that time. A few years later Drohocki (1938) used a manual amplitude integration method, which was performed automatically a decade later (Drohocki 1948). In 1943 Grey Walter introduced a frequency analyzer based on electronic band width filtering. However, it was not until the invention of digital computers that quantitative EEG analysis became easily accessible. Today, small extremely powerful computers are available at a cost, which has facilitated a much wider use of computerized EEG analysis in clinical neurophysiological laboratories.

The methods used in quantitative EEG analysis are of two main types (Burch 1959): Analysis in the *frequency domain*, where the periodicity of a given EEG pattern establishes its primary frequency components in which the amplitude is the quantitative unit (e.g. Fourier transformation); and analysis in the *time domain*, in which the time occurrence of specific EEG amplitude points is the quantitative unit (e.g. period analysis). The numerous methods of quantitative EEG analyses have recently been thoroughly reviewed (Rémond 1977).

EEG *period analysis*, in which the fre-

quency content is derived by accumulating the EEG waves in frequency classes according to the reciprocal periods measured between zero-crossings, was first performed automatically by Saltzberg and Burch (1957, 1959) on a hybrid special purpose "computer" and later on a general purpose digital computer (Burch et al. 1964). Various modifications of the principle of period analysis have been used by several investigators for quite different purposes (Legewie and Probst 1969; Roessler et al. 1970; Carrie and Frost 1971; Welch 1971; Obrist et al. 1973; Schenk 1975; Sharp et al. 1975; Cohen et al. 1976; Feinberg et al. 1980; Sotaniemi et al. 1980). The method has been advantageous especially in psychopharmacological and psychiatric research (Fink 1975; Itil 1975).

The *period-amplitude (P-A) analysis* used here (paper I) is based on earlier work and experience with both manual measurements and period analysis (Obrist 1963; Obrist et al. 1963; Thompson and Obrist 1964; Sulg 1969 a, 1969 b; Sulg et al. 1970) and simulates in many respects visual evaluation of the EEG background activity. In addition to paper I, which describes the computer programs, and papers II to VI which exemplify my application of P-A analysis in patients and healthy subjects, this thesis also contains EEG P-A analysis data de-

rived from a group of adult volunteers. This normal material has not previously been published, but part of it constitutes the control subjects in studies III, V and VI. For an appropriate scientific and cli-

nical use of the method, knowledge about the reliability of the P-A analysis and the EEG variability is a *sine qua non*. Therefore assessments of reliability and variability are included.

TECHNIQUE AND METHODOLOGY

Paper I gives a detailed description of the automatic data acquisition and the principle of computations used in the period-amplitude analysis program.

Analysis principles

In short, zero-crossings, peaks and troughs in the EEG signals are detected. From these points two types of EEG waves are measured: base waves, which cross the baseline, and superimposed waves, which do not cross it (Fig. 3 of paper I). Full wave measurements were used to eliminate the disturbing effect of randomly imposed low frequency activity with a low amplitude on a well-defined background activity. On the other hand this involves the possibility that high frequency activity with high amplitude might interfere with the analysis result by cutting lower frequency activity. However, the decision to measure full waves instead of half waves was made mainly because it brings the analysis principle closer to the conventional method of visual interpretation.

The period of the waves was measured by multiplying the number of sampling points in the digitized waves by the time interval (5 ms) between samples. Measured waves with a period outside the range 2,000 to 35 ms, corresponding to 0.5 to 28.6 Hz, were rejected.

The peak-to-peak amplitude of the waves was calculated from the RMS (root mean square) value assuming that the waves were sinusoidal. A special formula was derived to calculate the RMS values of superimposed waves (formula (4) and Fig. 4 of paper I). Waves with a peak-to-peak amplitude less than 3 μ V were rejected in accordance with the probable noise level of the EEG recording (Silverman et al. 1969).

The waves were classified and accumulated according to their period in 21 frequency classes covering the frequency range 0.5 to 28.6 Hz. The period and frequency limits of the classes, the class widths, and the center frequencies of the classes are shown in Table 1 of paper I. The percentage activity time (%AT), i.e. the accumulated periods in per cent of the analysis epoch, constitutes a frequency distribution (a histogram or a polygon) with the %AT along the ordinate and the center frequencies along the abscissa. A frequency distribution of the mean peak-to-peak voltage (MV) of each frequency class was done in the same way. The EEG mean frequency (MF) was calculated from the %AT frequency distribution. In addition, the EEG mean peak-to-peak voltage (MVA) of the total analysis epoch was calculated. P-A analysis results of a nor-

mal EEG are shown in Figs. 8 and 9 of paper I.

EEG recording/tape recording

The EEG was recorded bipolarly with surface or needle electrodes placed according to the international 10-20 electrode system (Jasper 1958). The derivations most commonly used were F3-C3, T3-T5, P3-O1, F4-C4 and P4-O2. The electroencephalograph was a Kaiser (papers II, III and part of the normal material) with input impedance of 10 M Ω or a Siemens Elema (papers IV, V, VI and normal material) with a differential input impedance of 1 M Ω . The time constant was 0.3 s, corresponding to a lower frequency limit of 0.5 Hz, and the upper frequency limit was 70 Hz. The electrode impedance was below 5 K Ω for the surface disk electrodes and below 10 K Ω for the platinum iridium needle electrodes. With the electroencephalographs used there should be no recording difference between the two electrode types (Zablow and Goldensohn 1969).

The electrocardiogram (ECG) and eye movement potentials were recorded simultaneously, the ECG from a surface electrode placed over the manubrium of the sternum, eye movement potentials from surface electrodes placed periorbitally. The submental (extralaryngeal) EMG activity (Berger 1961) was recorded to check wakefulness only in study IV, not in subsequent studies as it proved less useful than originally assumed.

Three to five EEG channels were simultaneously recorded on analogue tape and on paper. A Tandberg instrumentation tape recorder was used in study II, a Hewlett-Packard in study IV, and a Lyrec in studies III and VI. Apart from the EEG, each tape file contained an 8 Hz sinusoidal AC voltage with an amplitude corresponding to 100 μ V peak-to-peak, which was used for calibration purposes.

Preanalysis editing of the EEG record

Artifacts in the EEG were detected visually and in general only artifact-free parts of the EEG record were accepted for analysis. In practice, a record in which one or more channels were contaminated with, for example, muscle activity could be included. However, the EEG variables from an artifact-contaminated channel were never included in the subsequent statistical analysis. This is the main reason for the different number of observations in different EEG regions, e.g. in the normal material (see Addendum).

For each EEG to be analysed, a 50-100 s epoch (divisible into five separate sections) without artifacts was selected. The selected epochs were identified by marking pulses on one of the tape channels. If semiautomatic digitizing (p. 17 and paper V) was performed, a 20 s epoch was selected.

Automatic data sampling

The sampling frequency was 200 Hz. First, the 100 μ V peak-to-peak 8 Hz calibration voltage was digitized and stored in the computer. For each channel a calibration factor was calculated from the RMS value of the 8 Hz signal. Then, after automatic detection of the marking pulse, three channels of the selected EEG epoch were sampled. Before sampling, the EEG signal passed a 30 Hz low pass filter (3 dB at 30 Hz, 60 dB/decade). The present version of the data acquisition program employs a circular buffer which permits continuous data sampling simultaneously with data storage on disk.

Data sampling and EEG analysis were performed on an IBM 1800 computer. Except for a few system subroutines, the computer programs were written in FORTRAN IV language. In addition to P-A analysis, a Hjorth automatic EEG

analyzer (Hjorth 1970, 1973) was used in study IV.

Semiautomatic data sampling

As semiautomatic digitizing of EEGs by means of a pencil follower (paper V) has not previously been reported, a more detailed description will be given below. This method offers excellent possibilities of quantitating EEGs recorded before the computer era.

A computer program was developed to digitize the paper EEGs. The digitizing was performed by means of a semiautomatic co-ordinatometer (D-MAC pencil follower) interfaced with the IBM 1800 computer to work on line with it. The pencil follower is a special table with a servo position follower and a special pen which generates an electromagnetic field. By means of the servo systems, a sensor plate under the table followed the movements of the pen. An electromechanical signal indicates the position of the pen by an error detecting code (Petherick 1956) presented to the digital input of the computer.

Before digitizing, the EEG paper curve must be aligned, so that the EEG channels are parallel to the abscissa of the pencil follower. This is done manually by reading two different points on the marking channel of the paper trace into the computer. If the Y co-ordinates are not equal, the paper trace is moved a little and the co-ordinates read again. This procedure is repeated until the two Y co-ordinates are equal. More than one correction is rarely needed. In accordance with the computer instructions the pen is then moved along the EEG signal. If the pen is moved in jerks or too fast, the readings may be invalidated. In that event the program signals a message, and the digitizing is then resumed.

At a paper speed of 3 cm/s, a sampling frequency of 200 Hz corresponds to 0.15 mm between sampling points. As the smallest increment distance of the pencil

follower is 0.10 mm, the program registered co-ordinates with an interval of 0.3 mm in the direction of the abscissa, corresponding to a sampling frequency of 100 Hz. By interpolation the program calculates the missing data points, corresponding to a 200 Hz sampling frequency which is required by the P-A analysis program. This interpolation corresponds to a slight smoothing of the EEG signal, like the 30 Hz low pass filter used in the automatic data sampling. The digitized signals are directly stored in the same disk files as used by the automatic data acquisition program. The time required for the semiautomatic digitizing depends on the complexity of the EEG, especially the degree of fast activity, on the analysis length, and on the number of EEG channels. Three 20 s epochs took on an average one hour. This time also included subsequent analysis. The results of a comparison between the semiautomatic and the automatic digitizing are given in the subsequent paragraph.

Automatic versus semiautomatic data sampling

The same 20 s EEG epoch of the F3-C3 and the P3-O1 derivations was analysed from 10 subjects after automatic and semiautomatic data sampling, respectively.

The difference between automatic and semiautomatic data acquisition concerning the MF of the F3-C3 derivation ranged from -1.2 Hz to 1.0 Hz, $\bar{x} = 0.1 \pm 0.68$ Hz*; for the P3-O1 derivation from -0.5 Hz to 0.2 Hz, $\bar{x} = -0.1 \pm 0.23$ Hz. A variance ratio test showed that the MF difference variation of F3-C3 was significantly greater than that of the P3-O1 ($F = 9.4$, $p < 0.001$). The difference of

* Indicates, here and elsewhere, mean $\pm$ standard deviation.

MVA determined after automatic and semiautomatic data sampling of the F3-C3 derivation ranged from $-0.5 \mu\text{V}$ to $2.7 \mu\text{V}$, $\bar{x} = 1.1 \pm 1.09 \mu\text{V}$; for the P3-O1 derivation from $-0.2 \mu\text{V}$ to $2.6 \mu\text{V}$, $\bar{x} = 1.0 \pm 0.98 \mu\text{V}$. The MVA difference variation was the same for the F3-C3 and P3-O1 leads.

Reliability of P-A analysis and optimal analysis length

The reliability of the method was evaluated by an estimation of *accuracy* and *precision* (reproducibility). The primary measurement in P-A analysis is the time interval between two zero crossings or two peaks of the EEG. The accuracy (i.e. the deviation of the computed value from the true value) of this measurement is thus determined by the sampling frequency. With the sampling frequency of 200 Hz, the time interval between two successive data points was 5 ms. Table 1 in paper I shows that 5 ms correspond approximately to 0.5 Hz in the 10 Hz frequency class. Consequently, a 200 Hz sampling frequency gives a low accuracy of single wave measurements in the alpha and beta ranges. However, the accuracy tends to increase by the square root of the number of waves measured. Thus, the objection to the use of a low sampling frequency in period analysis which has been raised by Harner (1977) and Burger (1980) is of limited practical importance. Further, determination of MF from computer-generated monorhythmic sine waves (Sulg et al. 1969) was accurate to 0.01 Hz within the frequency range 0.5 to 28.6 Hz. This implies that P-A analysis must include a certain number of different wave measurements to establish reliable EEG parameters with an acceptable accuracy. Therefore, the optimal, i.e. the minimum analysis epoch has to be known. P-A analysis of 10 to 80 s epochs, followed by statistical evaluation of the MF and MVA diffe-

rence between equal epoch lengths, showed that the optimal analysis epoch was dependent on the EEG derivation used. Fronto-central derivations showed greater variability than parieto-occipital ones. An analysis epoch of 40 to 80 s frontally and 40 s occipitally appears optimal in normal subjects. The optimal analysis epoch would be shorter for an EEG dominated by low frequencies.

In studies II to IV and VI, in which I used automatic EEG sampling, at least 50 s epochs were analysed. In study V, where semiautomatic EEG digitizing was performed, I chose a 20 s epoch in accordance with Sulg (1969 a). Compared with variation of other causes, a decrease in variation achieved by increased analysis length was negligible.

The precision (i.e. the degree to which repeated analysis results agree) was considered both for automatic and semiautomatic data sampling. With *automatic data acquisition* the standard deviation of the differences between double determinations were 0.09 Hz and $0.2 \mu\text{V}$ for MF and MVA, respectively. With *semiautomatic digitizing* by pencil follower the standard deviations were 0.33 Hz and $0.8 \mu\text{V}$.

EEG variability

The *intra-individual variation* was considered as the *intra-record variation* i.e. the variation occurring in the course of a single recording and as the *day-to-day variation*, i.e. the variation from one day to the next. This latter variation is of particular importance during repeated measurements in clinical studies where small shifts of EEG may be significant.

The intra-record variation was assessed by analysing the variation due to selection of EEG sections for analysis. The standard deviations of the MF differences between two randomly selected sections of the same recording were 0.25 Hz and 0.34 Hz for fronto-central and parieto-occipital derivations, respective-

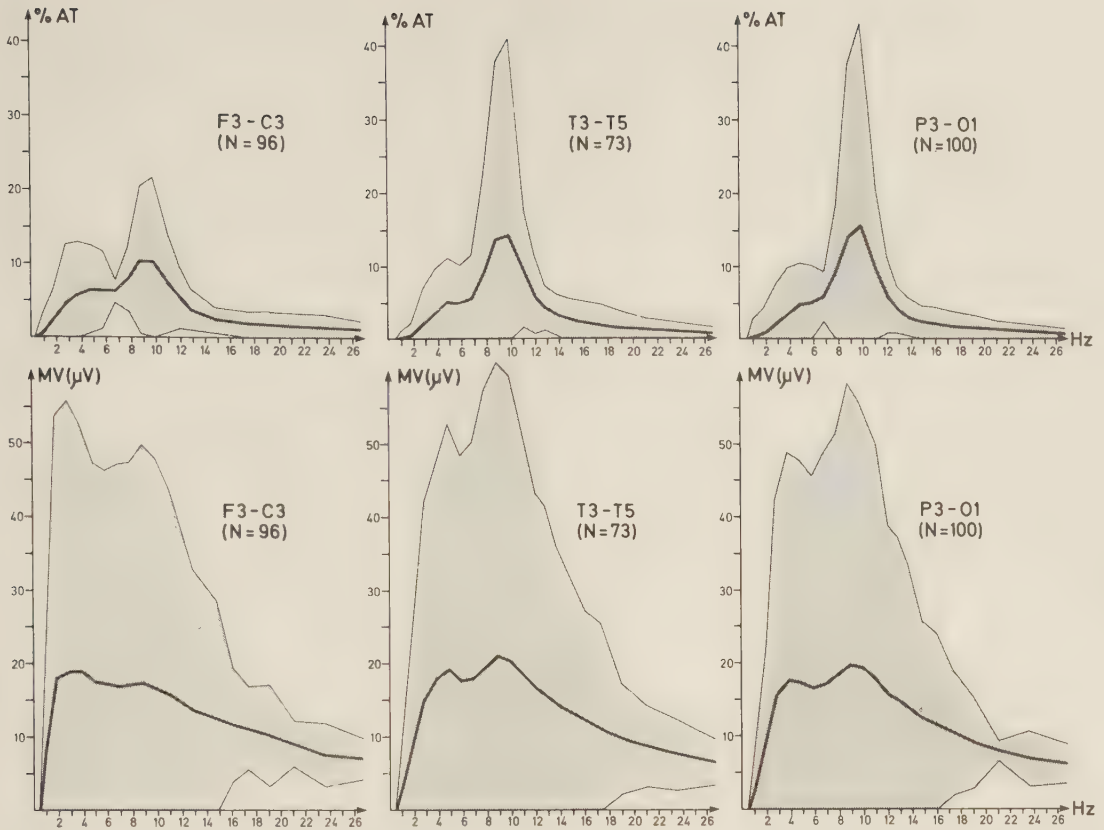


Fig. 1. Mean per cent activity time (%AT) and mean voltage (MV) frequency distributions from the left fronto-central, temporal, and parieto-occipital regions of 100 healthy subjects. The thick lines and the shaded areas represent the mean $\pm$ 2 standard deviations.

ly. The corresponding values concerning the MVA were $1.2 \mu\text{V}$ and $1.1 \mu\text{V}$.

The day-to-day variation was estimated by analysing two EEGs recorded one to five days apart. The standard deviations of the MF differences between two analyses carried out on different days were 0.73 Hz and 0.58 Hz for fronto-central and parieto-occipital derivations, respectively. The corresponding values for MVA were $0.92 \mu\text{V}$ and $3.2 \mu\text{V}$.

In conclusion, the analysis of the intra-individual variation showed that MF fluctuated about ± 1.5 Hz fronto-centrally and ± 1.2 Hz parieto-occipitally from one day to the next. These figures clearly exceed those found for precision and

intra-record variability, but are probably minimal values, as all recordings were done under optimal, controlled conditions. To keep this variability low, EEG studies have to be performed under strictly controlled and standardized conditions, as the variation is not due mainly to the analysis method or procedure, but is inherent in the EEG, caused by quantitative and qualitative alterations in the level of consciousness.

Normative EEG parameters and estimates of the *inter-individual variation* were obtained from a group of 100 healthy people (see Addendum).

Fig. 1 shows the mean per cent activity time (%AT) and the mean voltage (MV)

P3-01 (N = 100)

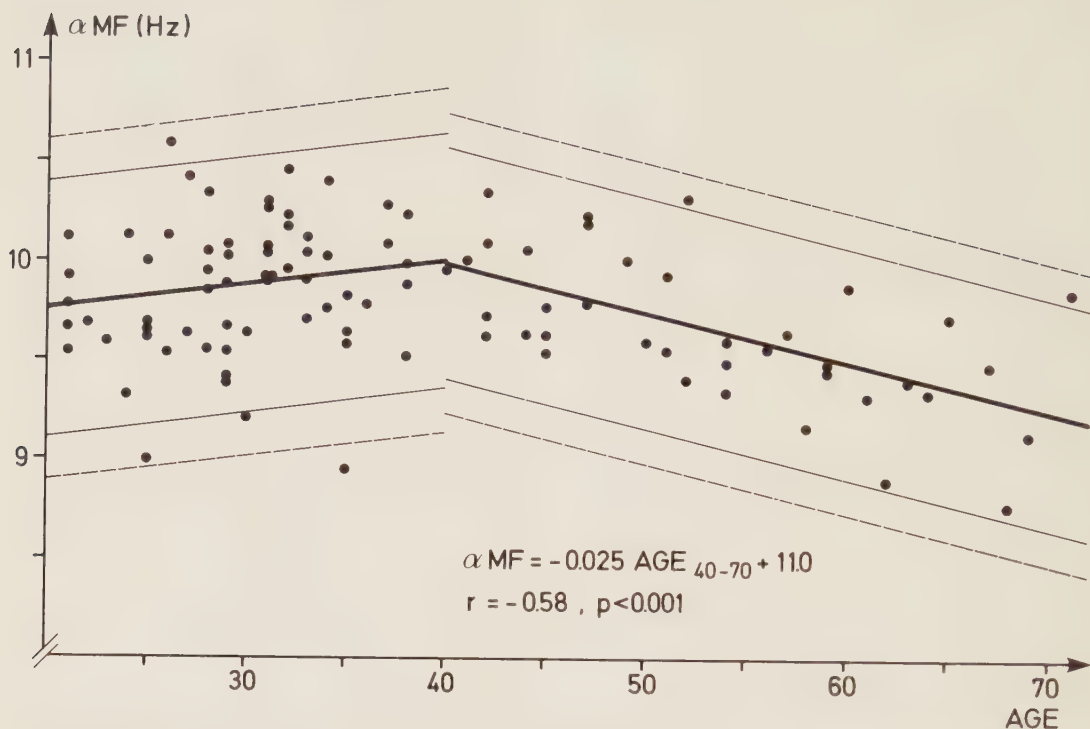


Fig. 2. Relation between parieto-occipital alpha mean frequency (α MF) and age in 100 healthy subjects. The regression line (thick line) is calculated by the least square method. The thin and stippled lines represent the 95 and 99 per cent confidence limits, respectively.

frequency distribution in the control subjects, measured in the left fronto-central, the left temporal, and the left parieto-occipital region. The average regional values of the MF, the MVA, the alpha mean frequency (α MF), and the alpha peak frequency (α PF) are given in the Addendum. The α MF and α PF values were similar to those derived by spectral analysis in adult males by Wierneke et al. (1980).

A highly significant negative correlation between α MF and age was found in the posterior regions, but not anteriorly. The quantity of slow (delta and theta) activity in the fronto-central regions tended to be less prominent with increasing age.

From 21 to 40 years of age there was no correlation between α MF and age,

whereas from 40 to 71 years the correlation was significant ($r = -0.58, p < 0.001$). The α MF decreased 0.3 Hz per 10 years during this period, estimated from the linear regression of Fig. 2. The MF or the quantity of alpha and beta activity did not correlate with age from 21 to 71 years.

Difference in sex had no significant effect on the EEG parameters or their variation, although the latter might have been expected due to the female menstrual cycle (Creutzfeldt et al. 1976).

P-A analysis compared with Hjorth and spectral analysis

In addition to P-A analysis, a *Hjorth analyzer* (Hjorth 1970, 1973) was used in study IV. Comparisons were done of the

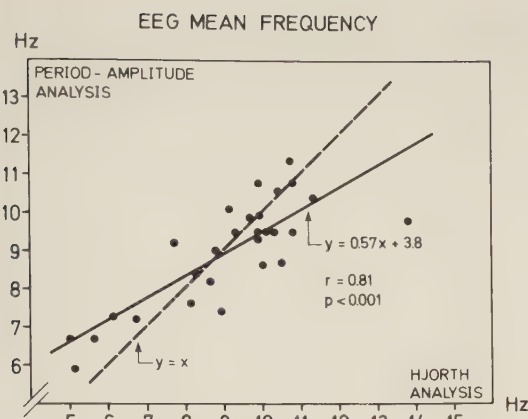


Fig. 3. Relation between EEG mean frequency (MF) and "mobility" (Hjorth analysis). Ten subjects with artifact-free EEGs from study IV. The regression line is calculated by the least square method.

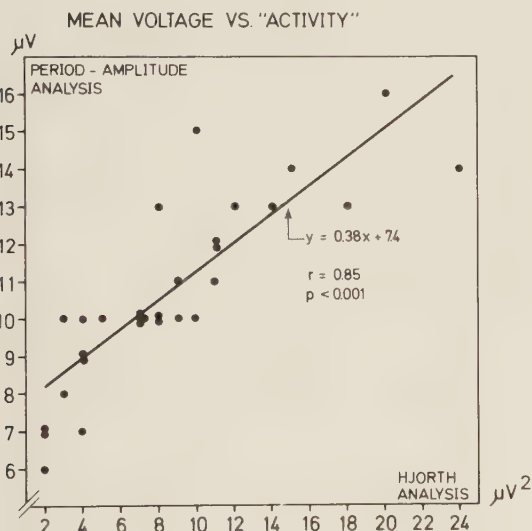


Fig. 4. Relation between EEG mean voltage (MVA) and "activity" (Hjorth analysis). The regression line is calculated by the least square method. Same subjects as in Fig. 3.

MF with the "mobility", which is another measure of mean frequency (the ratio between the standard deviation of the slope and the standard deviation of the amplitude), and of MVA with "activity", a measure of the mean power (amplitude variance), in the 10 subjects with artifact-free EEGs in study IV. Fig. 3

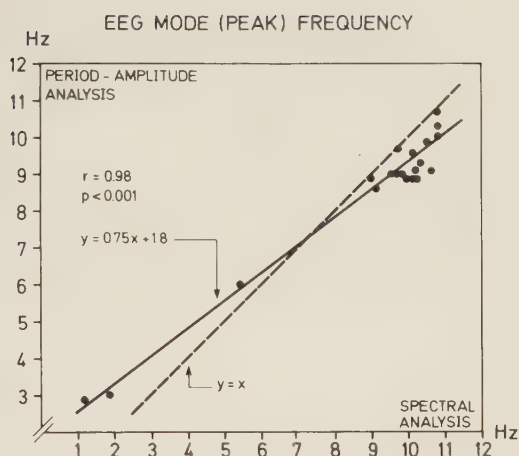


Fig. 5. Relation between EEG peak frequencies determined by P-A analysis and spectral analysis. Ten subjects selected at random from the normal material. The regression line is calculated by the least square method.

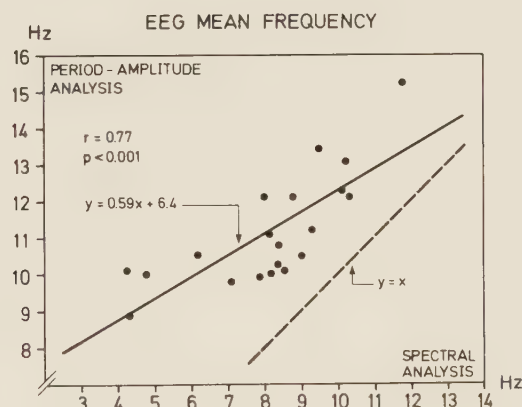


Fig. 6. Relation between EEG mean frequency (MF) and power spectral mean frequency. The regression line is calculated by the least square method. Same subjects as in Fig. 5.

shows the MF plotted against the "mobility". The two parameters correlated ($r = 0.81$, $p < 0.001$), but with a slight tendency to higher "mobility" values in the alpha and beta ranges and lower "mobility" values in the theta range. MVA and "activity" also correlated ($r = 0.85$, $p < 0.001$) (Fig. 4).

Moreover, P-A analysis and *spectral analysis* (Walter 1963) were compared. The power density spectrum was derived by fast Fourier transformation (Cooley and Tukey 1965) of the EEG*.

Mean and mode (peak) frequencies were calculated from the power density frequency distribution (power spectrum) and compared with the MF and mode

frequency of the P-A analysis. Within the alpha range, the mode of the power spectrum was slightly higher than that of the %AT frequency distribution, whereas in the delta-theta range the power spectral mode tended to be lower (Fig. 5).

The comparison of EEG mean frequencies (Fig. 6) showed a similar pattern, although all power spectral mean frequencies were lower than those of the P-A analysis. The reason is that the P-A analysis, like the visual EEG inspection, acts as a high-pass filter which does not take very low frequencies into account in the presence of a well-defined background activity.

*The analysis was performed on an ALPHA LSI 2/20 computer using a CED operative system in the Department of Audiology, Gentofte Hospital. The sampling frequency was 112 Hz, which resulted in a frequency resolution of 0.05 Hz within the alpha range.

P-A ANALYSIS APPLICATIONS IN PATIENTS

P-A analysis of the EEG was performed in two groups of patients: one with cirrhosis of the liver (paper II and III), and one with Pick's or Alzheimer's disease (paper V).

Patients with cirrhosis of the liver

The effect of lactulose on hepatic encephalopathy as evaluated by EEG P-A analysis (paper II). Eleven patients with cirrhosis of the liver and surgical portocaval anastomosis were examined clinically and by EEG P-A analysis. Ten of them were followed for four weeks, the EEG being recorded twice before and twice during treatment at an interval of four to five days, and finally once nine days after discontinuation of treatment. In a pilot study, one patient was followed for two months with 14 recordings.

The dominant EEG frequency, calculated as the mean of the five successive frequency classes containing most activity, was the main EEG parameter.

During treatment the EEG of four patients improved by an increased dominant EEG frequency and a shift towards higher normal frequencies in the %AT frequency distribution. These changes were followed by clinical improvement in three patients, all of whom had disturbances of consciousness. All patients

showing EEG improvement during lactulose treatment had had a reduced dominant frequency i.e. below 7.5 Hz (Fig. 4 of paper II), whereas those who did not improve in EEG had had a dominant EEG frequency above 7.5 Hz. This may indicate that liver detoxication in the latter patients was adequate despite the surgical portocaval shunt. However, routine liver function tests (plasma bilirubin, p-p time, alkaline phosphatases, albumin and gamma globulin) did not differentiate the two groups. The findings were in agreement with previous reports (Rorsman and Sulg 1970; Bircher et al. 1971) of improvement in hepatic disturbances of consciousness after lactulose treatment, but it does not answer the question, whether lactulose protects against encephalopathy or over a long time improves the chronic intellectual impairment.

A possible correlation between quantitative liver function and EEG was investigated in a group of 40 cirrhotic patients with and without surgical portocaval anastomosis, who had no disturbances of consciousness (paper III). Ten patients were examined before and after shunt operation and 14 only after being operated. Fourteen patients did not undergo surgery. Two patients were excluded because their EEGs were of the dys-synchronized low voltage type. Conse-

quently, there are 24 EEGs of patients without and 24 of patients with surgical portocaval anastomosis. Twenty-five age-matched healthy subjects served as controls. The %AT frequency distributions showed a shift towards lower frequencies from the control group to the unoperated cirrhotics and further to the operated ones (Fig. 1 of paper III). This shift was also reflected in the mean dominant frequencies of the groups.

The dominant EEG frequency correlated significantly with the liver function as expressed by the galactose elimination capacity (Tygstrup 1964) in all patients and also in the non-shunted group when considered separately. Such a correlation was not present in the shunted group. Thus, both liver function and porto-systemic shunting seem of importance to the reduced dominant EEG frequency seen in some cirrhotic patients. The predictive value of EEG with respect to estimating liver function and *vice versa* was limited, being restricted to a possible association of a galactose elimination capacity of less than 225 mg/min in non-shunted patients with a reduced dominant frequency (Fig. 2 of paper III). The shunting procedure reduces the liver function by approximately 10% (Kardel et al. 1975), but this explains only partly the significant 0.65 Hz median reduction of dominant EEG frequency after the shunt operation. Differences in the tolerance of the brain and in the amount of shunted toxic material may add to this reduction, but this has not yet been investigated.

Patients with Alzheimer's and Pick's diseases

In study V the results of EEG P-A analysis in neuropathologically verified cases of Alzheimer's and Pick's diseases (Brun and Gustafson 1976) were compared with the regional cerebral blood flow (rCBF) measured by the intra-arterial $^{133}\text{Xenon}$ clearance technique (Las-

sen and Ingvar 1972). The EEGs were compared with those of an age-matched group from the normal material.

The rCBF was measured in eight regions of the left hemisphere and compared with EEG parameters obtained from approximately the same regions (Fig. 1 of paper V) in four patients with Pick's disease and in six with Alzheimer's disease. Another three patients with Alzheimer's disease who had no rCBF measurements were included in the EEG analysis. All Alzheimer patients had severely generalized abnormal EEGs. However, the EEGs of the Pick patients also deviated significantly from those of the healthy controls, but to a lesser degree, showing increased delta and theta activity, mainly fronto-centrally, combined with preserved parieto-occipital alpha activity. This difference of EEG abnormality in Pick's and Alzheimer's diseases is of differential diagnostic importance. Regional computer EEG analysis, including measurements of the EEG pattern distribution of the hemispheres, may thus be useful in obtaining a differential diagnosis in organic dementia.

In the Pick patients the EEG mean frequency (MF) was highly correlated to the grey matter blood flow, whereas no consistent correlations between EEG and cerebral blood flow could be demonstrated in the Alzheimer patients, probably due to a different pathology in the two diseases. Taking all patients together, the slowing of MF correlated significantly with a reduction in white matter blood flow. Also, flow and EEG in the frontal and post-central regions ("pre-postcentral ratio", cf. Ingvar 1979; Ingvar et al. 1979) were highly correlated in the whole group. This indicates that interregional EEG relations reflect the interregional flow distribution in both types of dementia. Comparative studies of regional EEG, rCBF, and regional metabolism are needed to establish the overall relation between these factors in dementia.

P-A ANALYSIS APPLICATIONS IN NORMAL SUBJECTS

EEG P-A analysis was applied to ascertain possible EEG changes in normal subjects during mental activity (paper IV) and during transcendental meditation (paper VI).

EEG during memorizing and reasoning

Mental activity in a person awake is accompanied by increased regional cortical blood flow which indicates changes in local neuronal activity (Risberg and Ingvar 1973). To demonstrate concomitant EEG changes, the EEG of 18 subjects was recorded from some of the cerebral regions (left frontal, left temporal, and left occipital) which showed increased blood flow during the same tests as used previously by Risberg and Ingvar.

An auditory short term memory test revealed amplitude increases in the alpha, theta, and delta frequency bands over the left frontal region. During a visual reasoning test there was, in addition, an increased theta amplitude in the left temporal region. The auditory test tended to reduce alpha activity in all 3 regions, the visual test only occipitally. Concordant results were obtained with the Hjorth EEG analyzer (Hjorth 1970, 1973).

The study confirmed that mental activity causes changes in the EEG (Lege-

wie et al. 1969; Giannitrapani 1971; Gevins et al. 1979) and demonstrated that different types of mental activity were reflected in different regional EEG patterns. As the experimental design eliminated influences of visual and auditory stimulation and perception, increased theta and alpha amplitudes seem to reflect the electrical event in the cortex elicited by the particular mental activity. This was further supported by fundamental similarities between the present EEG findings and the rCBF patterns found previously (Risberg and Ingvar 1973).

EEG during transcendental meditation

It has been hypothesized that transcendental meditation (TM) induces a wakeful hypometabolic state different from an ordinary relaxed drowsy state (Wallace et al. 1971). However, electroencephalographic studies have been divergent. Wallace (1970) found an increased regularity and amplitude of the alpha activity during meditation, a finding which was supported by Banquet (1973). Later studies (Tebēcis 1975; Pagano et al. 1976; Fenwick et al. 1977), however, could not support the assumption of a unique state of consciousness with "specific" EEG changes.

As P-A analysis provides a sensitive means of distinguishing EEG changes caused by small shifts in consciousness (Itil et al. 1969; paper II), the method was applied in a quantitative and controlled study of the TM effect on the EEG (paper VI). The EEG was recorded during TM and compared with the EEG recorded during wakefulness, drowsiness, sleep onset and sleep in 14 persons with long-standing experience of the TM technique. In addition, the EEGs of the TM group were compared with those of an age-matched group from the normal material.

During TM the meditators were at a quantitative level of consciousness characterized electroencephalographically as a normal physiological state between wakefulness and drowsiness. They maintained this EEG pattern virtually unchanged during 20 min of meditation, a phenomenon quite different from their normal pattern of relaxation, which was characterized by fluctuations. This finding has recently been supported by Wachsmuth and Dolce (1980). The increased regularity and amplitude of alpha activity reported by Wallace (1970) during TM could not be confirmed. There was, however, a minor increase of theta and alpha amplitude in the left fronto-temporal region during TM. This might be imagined to be due to the inner speech used in TM, since similar EEG changes were recorded during mental activity (paper IV).

The EEG mean frequency of the TM group while not meditating was slightly slower (0.5 - 1.0 Hz) than that of the control group, a finding in accordance with Tebêcis (1975). This could either be a result of practicing TM or it might indicate that the TM group constitutes a selective population with a lower dominant EEG frequency. Tebêcis assumed that this was an effect of practicing TM which occurred gradually and progressed slowly during long-term practice. This suggestion was not supported by the present study, since the EEG frequency did not correlate with the duration of TM practice. However, a longitudinal design in a comparative study of inexperienced and experienced meditators would be needed to clarify this point.

Although the present study showed that the meditators are able to put themselves into a stable physiological state between wakefulness and drowsiness, it does not give any information concerning a possible mental influence of meditation. Further research, especially psychological, is needed to settle this problem. Our findings, however, could form a basis for such studies, since it is now possible to distinguish electroencephalographically persons who are meditating from persons who are otherwise relaxed.

GENERAL SUMMARY

In this study it was shown that EEG P-A analysis provides findings which are accurate and reliable. Its clinical and scientific significance was demonstrated in patients with cirrhosis of the liver, in patients with presenile dementia, and in normal subjects during mental activity and during transcendental meditation. In addition to control reference data in research work, the estimates of the normal intra- and inter-individual EEG variation constitute one prerequisite for the development of a useful clinical EEG analysis system.

Compared with spectral analysis, the method emphasizes activity in the alpha and theta bands and gives little impression of the low voltage, low frequency content of the normal EEG. This property of P-A analysis resembles the results of visual EEG interpretation and is considered an advantage, since the basis of clinical EEG evaluation can be applied directly to the analysis results.

The present system for data acquisition and analysis was highly satisfactory for the purposes of this study. However, the laborious procedure of tape recording, visual artifact elimination, data sampling and analysis is hardly suited to clinical practice. For that purpose the system requires modifications and extensions, both in software and hardware, which are indeed accessible to day, both technically and economically.

One important factor in computerized EEG analysis is artifact detection and elimination. A number of different methods exist for automatic or semiautomatic artifact rejection (Ktonas et al. 1979), but no method is as good as the eyes and mind of the experienced electroencephalographer. Therefore, a careful visual input and output control is to be recommended even though automatic artifact rejection is incorporated in the analysis system.

The present P-A analysis quantitates the EEG background activity. For clinical use the analysis must inevitably include transient activity detection and paroxymal wave shape characterization. Period analysis based methods for this purpose have already been developed (Carrie 1972; Ehrenberg and Penry 1976; Gotman and Gloor 1976).

A suitable user-oriented, hard-copy result presentation must also exist. The group comparison presentation on which this study has focused is not sufficient, as the main task in daily routine is serial electroencephalography (Matousek et al. 1979).

Hardware improvements would facilitate these desirable software modifications. As the analysis principles and the calculations are fairly simple, even microprocessors have sufficient spare time during execution to sample data, detect artifacts, and preprocess multichannel

EEG signals in true time (Dumermuth and Dinkelmann 1979; Frost et al. 1980; Salb 1980). However, the subsequent processing of the analysis results would benefit from the use of a minicomputer which, interfaced with satellite micro-processors, would provide a flexible sy-

stem with sufficient storage, access to disk and display facilities to handle serial clinical electroencephalography. Further program development and modification would be highly facilitated by such a configuration.

ADDENDUM: Reliability of P-A analysis and EEG variability

Accuracy

Period analysis of monorhythmic computer generated sinewaves (20 s epochs) was compared with the known "true" frequencies of the sinewaves. The true frequencies ranged from 2 Hz to 28 Hz, the MF from 1.999 to 27.998. The differences between MF and the true frequencies were from 0.001 Hz to 0.010 Hz, $\bar{x} = 0.004 \pm 0.003$ Hz. Expressed in per cent of the true frequencies, the difference ranged from 0.01% to 0.05%, mean 0.03%.

Analysis epoch length

Two successive 10 s, 20 s, 40 s, and 80 s EEG epochs from 10 healthy subjects were analysed. The MF variation of the F3-C3 derivation, expressed as the standard deviation of the differences between epochs of the same length, was 0.50 Hz, 0.62 Hz, 0.56 Hz, and 0.25 Hz, for 10 s, 20 s, 40 s, and 80 s respectively. A variance ratio test showed that the variation of the MF differences was significantly lower for the 80 s epochs than for the shorter epochs ($F = 4.17$, $p < 0.05$). For the MVA differences the variation was the same for 10 s and 20 s epochs, but significantly lower for the 40 s and 80 s epochs ($F = 4.30$, $p < 0.05$).

In the P3-O1 derivation the standard deviations ranged from 0.23 Hz to 0.36 Hz. The variation of MF differences could not be reduced by increasing the analysis epoch from 10 s to 80 s. However, the MVA variation was significantly lower with 40 s and 80 s epochs than with 10 s and 20 s epochs ($F = 3.96$, $p < 0.05$).

Precision (automatic data acquisition)

The precision was tested by double determination of MF and MVA in the P3-O1 derivation of 25 healthy subjects (100 s epochs). The difference between first and second determination of MF ranged from -0.15 Hz to 0.19 Hz, $\bar{x} = 0.006 \pm 0.086$ Hz, the MVA difference from -0.25 μ V to 0.35 μ V, $\bar{x} = 0.03 \pm 0.15$ μ V.

Precision (semiautomatic data acquisition)

Double determinations were done in 20 s epochs of the P3-O1 derivation in 20 subjects. The differences between first and second determination of MF ranged from -0.65 Hz to 0.50 Hz, $\bar{x} = -0.10 \pm 0.33$ Hz, the MVA difference from -1.6 μ V to 2.0 μ V, $\bar{x} = -0.04 \pm 0.8$ μ V.

Intra-record variation

In 10 subjects, two 80 s epochs from the F3-C3 and the P3-O1 derivations of the same EEG were analysed. The difference between the fronto-central MF of the first and second analysis ranged from -0.31 Hz to 0.44 Hz, $\bar{x} = 0.01 \pm 0.25$ Hz. The parieto-occipital MF difference ranged from -0.46 Hz to 0.74 Hz, $\bar{x} = 0.02 \pm 0.34$ Hz. The corresponding values concerning the MVA were for F3-C3: -2.1 μ V to 2.2 μ V, $\bar{x} = 0.3 \pm 1.19$ μ V, and for P3-O1: -1.0 μ V to 2.7 μ V, $\bar{x} = 0.8 \pm 1.06$ μ V.

Day-to-day variation

In 10 subjects, the EEG was recorded twice, at least one day and maximum five days apart. 100 s epochs from the F3-C3 and the P3-O1 derivations were compared. For the F3-C3 the MF difference between the first and second day ranged from -0.94 Hz to 1.13 Hz, $\bar{x} = -0.06 \pm 0.73$ Hz, the parieto-occipital MF difference from -0.96 Hz to 0.92 Hz, $\bar{x} = -0.13 \pm 0.58$ Hz. The corresponding values concerning the MVA were for the F3-C3: -0.7 μ V to 2.5 μ V, $\bar{x} = 0.6 \pm 0.92$ μ V, and for the P3-O1: -7.2 μ V to 4.7 μ V, $\bar{x} = 0.02 \pm 3.20$ μ V.

Inter-individual variation

A control group consisting of 100 healthy subjects (59 females and 41 males, median age 34 years, range 21-71 years) was analysed. All subjects had normal birth

and no history of neurological disease or head injuries with cerebral symptoms. Except for six females on oral contraceptives, none was on medication. No subjects had a daily alcohol consumption, and no alcohol was taken for the last 24 hours before the EEG study. All subjects were active in their normal work.

The mean regional values of the MF, the MVA, the alpha mean frequency (α MF), and the alpha peak frequency (α PF) are shown in table 1.

The mean *inter-hemispheric* MF difference fronto-centrally was 0.43 Hz, SD = 0.75 Hz, significantly ($p < 0.05$) higher on the left side. Parieto-occipitaly it was 0.14 Hz, SD = 0.67 Hz. This latter difference is not significant.

The mean *intra-hemispheric* MF difference, expressed as the ratio between the fronto-central and the parieto-occipital region was 1.01, SD = 0.12, and 0.99, SD = 0.10 left and right hemisphere, respectively.

Age relationship

The alpha mean frequency (α MF) and the alpha peak frequency (α PF) correlated negatively with age, $r = -0.33$, $p < 0.001$ for temporal and parieto-occipital regions, respectively. There was no correlation fronto-centrally. Except for a negative correlation between age and the quantity of delta and theta activity in the fronto-central regions ($r = -0.23$, $p < 0.05$), no association between age and other EEG parameters could be demonstrated.

TABLE 1. EEG mean frequency (MF), alpha mean frequency (α MF), alpha peak (mode) frequency (α PF), and EEG mean voltages (MVA) in the fronto-central, temporal, and parieto-occipital regions of 100 healthy subjects. Normal limits, expressed as the mean $\pm$ 2 standard deviations, are indicated. The normal limits of MVA are derived from the log transformed values.

EEG DERIVATION	n	MF (Hz) $\bar{x} \pm$ SD (normal limits)	α MF (Hz) $\bar{x} \pm$ SD (normal limits)	α PF (Hz) $\bar{x} \pm$ SD (normal limits)	MVA (μ V) $\bar{x} \pm$ SD (normal limits)
F3-C3	96	11.3 $\pm$ 1.55 (8.2-14.4)	9.8 $\pm$ 0.28 (9.2-10.3)	9.3 $\pm$ 0.95 (7.4-11.2)	14 $\pm$ 5.1 (6 - 26)
F4-C4	78	10.7 $\pm$ 1.45 (7.8-13.6)	9.7 $\pm$ 0.29 (9.1-10.3)	9.1 $\pm$ 0.80 (7.5-10.7)	13 $\pm$ 4.1 (7 - 22)
T3-T5	73	11.5 $\pm$ 1.40 (8.7-14.3)	9.8 $\pm$ 0.36 (9.1-10.5)	9.5 $\pm$ 0.82 (7.8-11.1)	17 $\pm$ 8.3 (6 - 35)
P3-O1	100	11.1 $\pm$ 1.24 (8.7-13.6)	9.8 $\pm$ 0.37 (9.0-10.5)	9.5 $\pm$ 0.82 (7.9-11.1)	16 $\pm$ 7.4 (6 - 34)
P4-O2	79	10.9 $\pm$ 1.17 (8.5-13.2)	9.8 $\pm$ 0.37 (9.1-10.5)	9.6 $\pm$ 0.79 (8.0-11.2)	16 $\pm$ 6.9 (6 - 33)

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ORIGINAL PAPERS I – VI

AUTOMATIC DATA ACQUISITION AND PERIOD-AMPLITUDE ANALYSIS OF THE ELECTROENCEPHALOGRAM

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Automatic data sampling of tape recorded EEG and subsequent quantitative analysis are performed on a general purpose digital computer (IBM 1800). An analysis epoch of 100 sec is selected from 3 channels of the EEG which after analog-to-digital conversion are stored on the disk storage unit of the computer. The digitized EEG is then analysed in accordance to a modified baseline crossing method. A calculation of quantitative parameters is performed based on the measured period, amplitude and energy content of the EEG waves.

Neurophysiology
Computers, digital

Electroencephalography
Automatic data processing

1. Introduction

The aim of the present paper is to describe a method for an on-line data acquisition and subsequent off-line period-amplitude analysis of the electroencephalogram (EEG) on a general purpose digital computer.

The programs perform an automatic digitizing and storage of maximum 100 sec EEG from 3 channels. An analysis in the time domain basically similar to the methods of Burch and others [1–3] is performed. The method has been used in clinical studies concerning the evaluation of drug effects and metabolic coma [4–5].

2. Preliminary processing

The analysis program does not recognize artefacts in the EEG (eye movements, muscle potentials, electrode errors etc.). For this reason it is necessary by visual judgement to exclude artefacts from that part of the EEG which has to be analysed. In order to

satisfy this requirement the EEG was recorded simultaneously on magnetic tape and on paper.

2.1. The EEG paper trace

Eight channels of the EEG machine (frequency range 0.5–70 cps) are used for the recording of an EEG for the period-amplitude analysis (fig. 1). Surface electrodes placed according to the "ten-twenty" electrode system [6] are employed. Channels 9–14 on fig. 1 are replay from the tape recorder. In these channels the EEG has passed through a 30 cps low pass filter. The lower limit is 0.5 cps corresponding to an amplifier time constant of 0.3 sec.

2.2. Editing of the EEG record for analysis

Three channels can be analysed simultaneously. Maximum 5 sections of EEG without artefacts with a total duration of 100 sec is selected for analysis (the normal used analysis epoch). The time (in seconds) from a given marking pulse (fig. 1) on channel 5 (the marking channel) to the selected section(s) and the

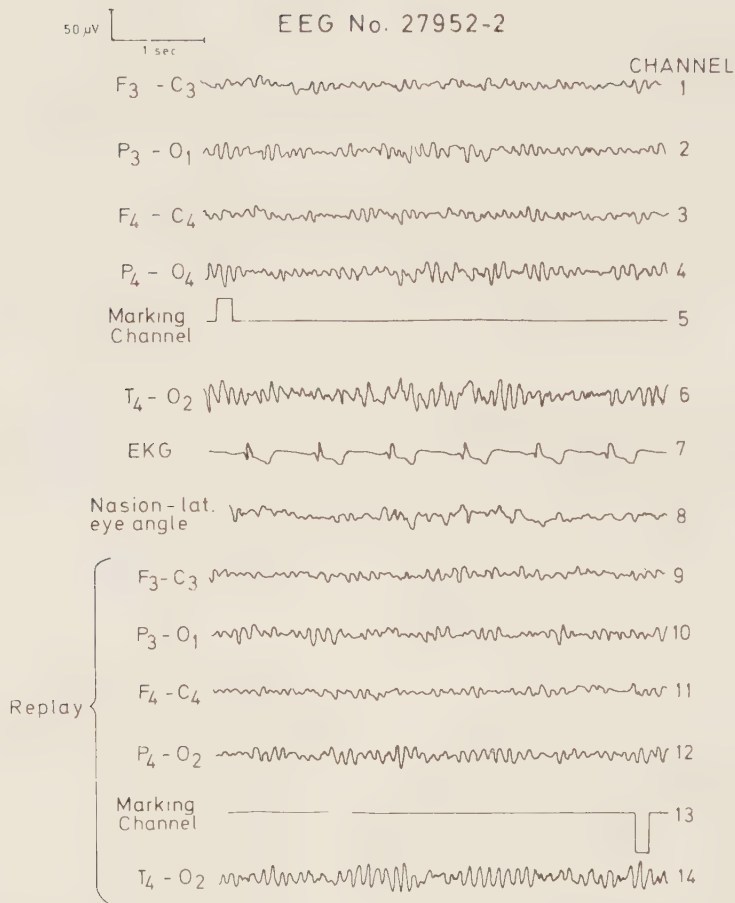


Fig. 1. Part of the EEG trace used for the sample run. Channels 1–8 represent direct recordings, channels 9–14 are replay from the tape recorder.

length of the respective section(s) is registered for use in the automatic data acquisition.

2.3. The EEG tape file

EEG from 5 different leads and one marking channel are recorded on a 6 channel tape recorder (tape speed $1\frac{7}{8}$ inch per sec) (fig. 2). The output from the tape recorder is 2 V peak-to-peak. This corresponds to 100 μ V peak-to-peak input to the EEG machine. Each tape file contains on all 6 channels about 20 sec

of an 8 cps sinusoidal AC voltage with an amplitude corresponding to 100 μ V peak-to-peak, from which a calibration factor for each channel is calculated.

3. Computational methods

3.1. The data acquisition program (the on-line part)

A general description of the control system of the computer, its time-sharing and communication facili-

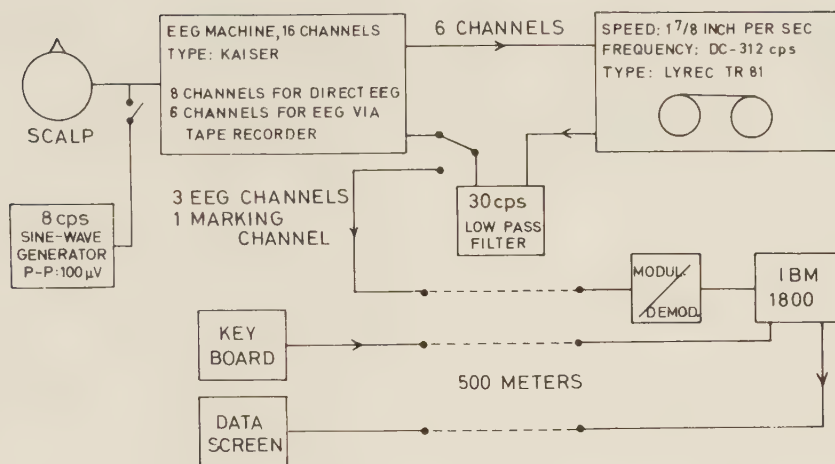


Fig. 2. Block diagram showing the measurement set-up.

ties are given in previous reports [7, 8]. This part of the main program consist of 3 subprograms linked together by means of Fortran call statements:

- (1) Keying in of identification of the EEG record and time variables for use in the final part of the program.
- (2) Sampling of calibration curves and computation of calibration factors.
- (3) Sampling, conversion and storage of the EEG-signals.

3.1.1. Digital input

The program examines whether there is an empty disk file (4 are predefined). In this case an EEG identification number is keyed in. This is done by a communication key board placed in the EEG laboratory and connected to the digital input channels of the computer system. The delay in seconds after a marking pulse on the marking channel to the preselected EEG sequences and their length are keyed in. The program searches for sequence and time interval errors. The keyed in data are successively shown on a data screen placed in the EEG laboratory and connected to the digital-to-analog converter of the computer (fig. 2). This enables visual control and correction of input data. For text display on the data screen system subroutines developed by the Department for Data Processing in Medicine, Gentofte Hospital have been used.

3.1.2. Calibration

A $100 \mu\text{V}$ peak-to-peak 8 cps sinusoidal voltage is used as calibration voltage. From each channel to be analysed, 3 sec of the prerecorded calibration voltages are sampled with the same sampling frequency as the EEG-signal (200 cps). An analog input subroutine AIX is used for the analog data sampling with simultaneous analog-to-digital conversion. This subroutine is described in the succeeding paragraph. The root mean square (RMS) value of the digitized calibration voltages are used to calculate a calibration factor for each channel which is used in the analysis program with correction of amplitude measurements.

3.1.3. EEG data acquisition

The EEG signal is transmitted through cables from the EEG laboratory to the computer center (distance approximately 500 m). A modulator-demodulator is used to achieve galvanic separation (fig. 2). The marking pulse on the marking channel is detected by means of a subroutine MARK(I). The input parameter I (an integer variable) is the logical number of the analog input channel connected with the marking channel.

When a marking pulse is detected, a hardware timer of the computer is initiated. By comparison of the timer status and the keyed in time variables the initiation of the data sampling is determined. The analog input subroutine employs 2 buffers, each with

a capacity corresponding to 1 sec of EEG. These buffers are successively filled. While one buffer is being filled up, data from the other is processed and stored.

With a sampling frequency of 200 cps, 100 sec EEG from 3 recorded channels corresponds to 60,000 data points. These are stored on one of the disk files.

In this part of the program, the following subroutines developed by IBM [9] have been used:

- DEFER A system subroutine used to initiate a machine interval timer.
- CANCL A system subroutine used to stop a machine interval timer before it has timed out.
- BULKN * A system subroutine which performs the writing of data on the disk storage unit.

Furthermore, the following system subroutine developed by the Department for Data Processing in Medicine, Gentofte Hospital has been used:

- AIX A system subroutine which controls the sampling and analog-to-digital conversion of analog signals. Simultaneous sampling from 8 input channels is possible. Minimum sampling interval is 0.25 msec determined by the smallest increment of the hardware timers.

3.1.4. Control of the EEG acquisition

Based on the status of the hardware timers in the beginning and at the end of the data sampling, the real initiate time and the duration of the sampling is calculated. The values are compared with the input parameters as control of a successful completion of the EEG data acquisition.

3.2. The EEG analysis program (the off-line part)

Like the acquisition program, the analysis program consist of 3 subprograms linked together by means of Fortran call statements.

- (1) Determination of the EEG baseline.
- (2) Analysis of the EEG-signal by measurement of baseline crossings and wave peaks. Calculation of the EEG wave period, amplitude and energy content.

* In the used MPX version 2 this subroutine is incapable of writing in a file protected area. For this reason it is necessary to define the disk files in a way that removal of the file protection is possible before the routine is used.

- (3) Processing of the primary analysis results:

- (a) Accumulation in matrices for the respective frequencies.
- (b) Summing in frequency bands.
- (c) Calculation of quantitative EEG parameters.

3.2.1. The EEG baseline

The analysis principle is partly based on a registration of intersection points between the EEG-signal and its baseline. A baseline for each channel is calculated as an arithmetic mean value of sampling points corresponding to a 10 sec epoch. As baseline reference the mean value between the calculated baseline for the first and last 5 sec of the EEG recording is employed. Drift of the channels is negligible as the EEG is an AC voltage. Therefore the calculated baseline for the first 5 sec has to be approximately equal to the baseline calculated from the last 5 sec.

3.2.2. Principle of analysis

Two different types of EEG waves are detected and measured: Basewaves and superimposed waves i.e. waves which cross the baseline and waves which do not cross it, respectively (fig. 3). The principle of whole period measurement is used in order to eliminate the troubling effect of randomly imposed low frequency activity (no high pass filter is employed) with small amplitude on a well defined background activity. On the other hand this gives the possibility that high frequency activity with high amplitude is able to interfere with the analysis result, by "cutting" lower frequency activity.

Analysis of computer simulated complex wave patterns, where the original oscillatory components

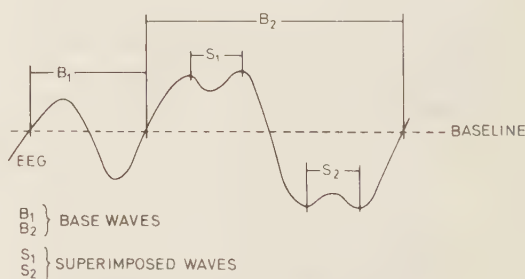


Fig. 3. Measuring principle of the EEG wave period.

(sine waves) were known and mathematically defined [10], demonstrated that the measurement of full waves were superior to that of half waves. Also, an analysis on full waves brings the principle closer to the conventional method of visual interpretation.

Concerning each measured wave the following variables are calculated: The period, the amplitude and the energy content.

3.2.2.1. Measurement of the EEG wave period. The period of a basewave is determined by the time between two successive negative to positive crossings of the EEG baseline. The period of a superimposed wave is determined by the time between two peaks or two valleys in the EEG-signal respectively (fig. 3). The measurements are performed on numerical values of the data points, corresponding to a folding of the EEG-signal about its baseline. In that way it is only necessary to measure peaks in the signal. Based on the number of sampling points in the digitized EEG wave and the sampling frequency (200 cps), the period of the wave is calculated in msec. Waves with a period outside the range 2000–35 msec corresponding to 0.5–28.6 cps are rejected.

3.2.2.2. Measurement of the EEG wave amplitude. The peak-to-peak amplitude is computed from a calculation of the RMS value of the EEG wave, making the approximation that the wave is sinusoidal.

$$\text{RMS} = \sqrt{\frac{\sum_{i=1}^m y_i^2}{m}} \quad (1)$$

where y is the amplitude value of a sampling point and m is the number of sampling points in the wave. The peak-to-peak amplitude A is equal to

$$A = \text{RMS} \cdot 2\sqrt{2}. \quad (2)$$

Concerning the basewaves the amplitude is calculated from the above mentioned formulars, while the problem of measuring the amplitude of superimposed waves in unfiltered EEG is complex. The following method is suggested by one of the authors (BS). Fig. 4 shows a part of an EEG-signal with a superimposed

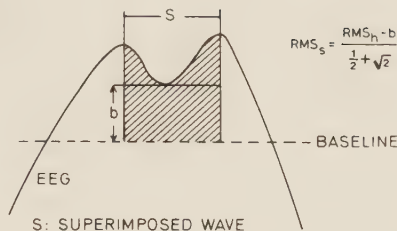


Fig. 4. Method of measuring the amplitude of a superimposed wave. For details see text.

wave. The RMS value calculated from the hatched part of the figure is called RMS_h . In order to eliminate the effect of the carrying basewave, RMS_h must be corrected for the linear voltage b and for the unknown amplitude of the superimposed wave a , thus attaining half the RMS value of the superimposed wave (RMS_s)

$$\frac{\text{RMS}_s}{2} = \text{RMS}_h - (a + b). \quad (3)$$

RMS_s is then obtained by the following equation as $a = \text{RMS}_s \sqrt{2}$

$$\text{RMS}_s = \frac{\text{RMS}_h - b}{\frac{1}{2} + \sqrt{2}}. \quad (4)$$

The peak-to-peak amplitude is then calculated from eq. (2). This is an approximation as the wave is superimposed on an unstable and undefined baseline. The amplitude measurement is also tested by analysis of the above mentioned computer simulated complex wave patterns. The calculated peak-to-peak amplitude is corrected to μV by multiplication with the calibration factors mentioned in sect. 3.1.2. Waves, on background as well as superimposed, with a peak-to-peak amplitude less than $3 \mu\text{V}$ are excluded in accordance with the probable noise level suggested by Silverman et al. [11].

3.2.2.3. Computation of the EEG wave energy content. An estimation of the total electrical energy E of a single EEG wave [16], still making the approximation that the wave is sinusoidal, is given by the following equation:

$$E = \frac{RMS^2}{f}$$

where *f* is the frequency in cps. For practical reasons the dimension used for energy is $\mu V/\sqrt{\text{cps}}$.

This is seen by squarring and succeeding integration of the periodic time function of a single sine wave:

$$F(t) = a \sin(\omega t) \, dt$$

where *a* is the amplitude, ω the angular velocity and *t* the time. As $a = RMS/\sqrt{2}$ one gets

$$\int_0^{2\pi} F(t)^2 \, dt = \int_0^{2\pi} 2 \, RMS^2 \sin^2(\omega t) \, dt = \frac{2 \, RMS^2 \pi}{\omega} = \frac{RMS^2}{f}$$

as $\omega = 2\pi f$.

3.2.3. Processing of the analysis results

According to the measured period the waves are classified and accumulated in 21 frequency classes. Table 1 shows the used frequency classes, class widths

and center frequencies. As shown the employed sampling frequency does not allow accurate class widths, especially in higher frequency classes. At the succeeding graphic representation of the frequency polygons the content in each class is corrected to a value corresponding to the width 1 cps. For each frequency class the following variables are calculated (abbreviations in agreement with the labels used in fig. 8):

- (1) The mean wave count (WAVE COUNT) per second analysis time.
- (2) The per cent activity time (PCT-TIME) [12-15], which is the activity time in per cent of the total length of the analysed EEG, i.e. the analysis epoch.
- (3) The mean voltage (MEAN VOLT) of each frequency class.
- (4) The mean energy (RMS/ROOT(HZ)) of each frequency class.

In addition the following parameters concerning the analysis are computed:

- (1) The total number of waves (TOTAL WAVE COUNT).

Table 1
Frequency classes, class widths and center frequencies used in the analysis. Waves with a period equal to a italicized figure are included in the respective class

Class cps	Period msec	Frequency cps	Width cps	Center frequency cps
1	2000-670	0.50- 1.49	0.99	1.0
2	670-405	1.49- 2.48	0.99	1.9
3	405-290	2.48- 3.47	0.99	2.9
4	290-225	3.47- 4.45	0.98	3.9
5	225-185	4.45- 5.41	0.96	4.9
6	185-155	5.41- 6.45	1.04	5.9
7	155-135	6.45- 7.41	0.96	6.9
8	135-120	7.41- 8.34	0.93	7.9
9	120-105	8.34- 9.53	1.19	8.9
10	105- 95	9.53-10.52	0.99	10.0
11	95- 85	10.52-11.78	1.26	11.2
12	85- 80	11.78-12.50	0.72	12.1
13	80- 75	12.50-13.34	0.84	12.9
14	75- 70	13.34-14.29	0.95	13.8
15	70- 65	14.29-15.40	1.11	14.9
16	65- 60	15.40-16.68	1.28	16.1
17	60- 55	16.68-18.19	1.51	17.4
19	55- 50	18.19-20.00	1.81	19.1
21	50- 45	20.00-22.21	2.21	21.1
24	45- 40	22.21-25.00	2.79	23.6
27	40- 35	25.00-28.59	3.59	26.8

- (2) The wave count, the summed per cent activity time, the mean voltage and the mean energy in 1–3 cps (delta), 4–7 cps (theta), 8–12 cps (alpha) and 13–27 cps (beta) frequency bands.
- (3) The total per cent activity time (TOTAL PCT-TIME) which is the total accumulated periods of the waves registered in the analysis in per cent of the analysis epoch.
- (4) The mean period (AVG. PERIOD) [16],

$$\text{AVG. PERIOD} = \frac{\text{TOTAL PCT-TIME}/100}{\text{TOTAL WAVE COUNT}}$$

- (5) The mean period frequency (AVG. FREQ) which is the reciprocal to the mean period and equivalent to the EEG frequency index given by Sulg [10].
- (6) The mean voltage of the analysis epoch.
- (7) The mean energy of the analysis epoch, equivalent to the EEG energy index according to Sulg [16].
- (8) The ratio between the number of superimposed waves and basewaves as an expression for the complexity of the EEG.

4. Flowcharts

In figs. 5, 6 and 7 system flowcharts of the mentioned programs are shown. The flowchart in fig. 5 applies to the EEG data acquisition part, those in figs. 6 and 7 to the EEG analysis part.

5. Sample run

For the sample run a 100 sec analysis epoch of a normal EEG has been stored on disk. From the computer console the wanted EEG is selected for analysis. The printer output from the analysis is shown in fig. 8. Besides the printer output the program punches 3 sets of output cards for each channel which contain the following variables (abbreviations in agreement with fig. 7):

- (1) (a) The per cent activity time (PCT-TIME) data throughout the 21 frequency classes.
- (b) The mean period frequency (AVG. FREQ).
- (2) (a) The mean voltage (MV/CLASS) data throughout the 21 frequency classes.
- (b) The mean voltage (MEAN VOLT) of the

analysis epoch.

- (3) (a) The mean energy (ME/CLASS) data throughout the 21 frequency classes.
- (b) The mean energy (MEAN ENERGY) of the analysis epoch.

A completion of the analysis output with polygon plottings [17] is possible. Fig. 9 shows for one channel the per cent activity time polygon and the corresponding mean voltage polygon. The employed plotter subroutine subprogram utilizes relocatable plotter subroutines developed by IBM [18].

The average time requested for the data acquisition part resulting in storage of a 100 sec epoch of EEG on disk was approximately 5 min. This considerably long time depends partly on the number of artefacts in the EEG record which has to be omitted, partly on the operation of the analog tape recorder and communication with the computer. The process time for the analysis which depends mainly on the complexity of the EEG was about 9 min without plotter output. Plotter display required further 5 min. These figures are not absolute values as a batch processing job has the lowest priority in the system monitor. Therefore it can be interrupted several times during execution.

6. Hardware and software specifications

The programs are coded in IBM 1800 FORTRAN IV LANGUAGE and executed on an IBM 1800 Data Acquisition and Control System utilizing the IBM 1800 Multiprogramming Executive Operative System (MPX), version 2 at the Department for Data Processing in Medicine, Gentofte Hospital. The subprograms linked together are independent apart from defined common areas. In that way the core requirement is determined by volume of the largest subprogram. To give an idea of the size of the program (inclusive the described subroutine subprograms) it may be mentioned that the source program consists of approximately 2000 Fortran statements. All programs are stored on disk.

The computer is a 32 K, 16 bits/word computer with a disk storage capacity of 1536 K. It is equipped with the following input/output units: IBM 1442 Card Read Punch, IBM 1443 Printer, IBM 1627 Plotter and IBM 2310 Disk Storage.

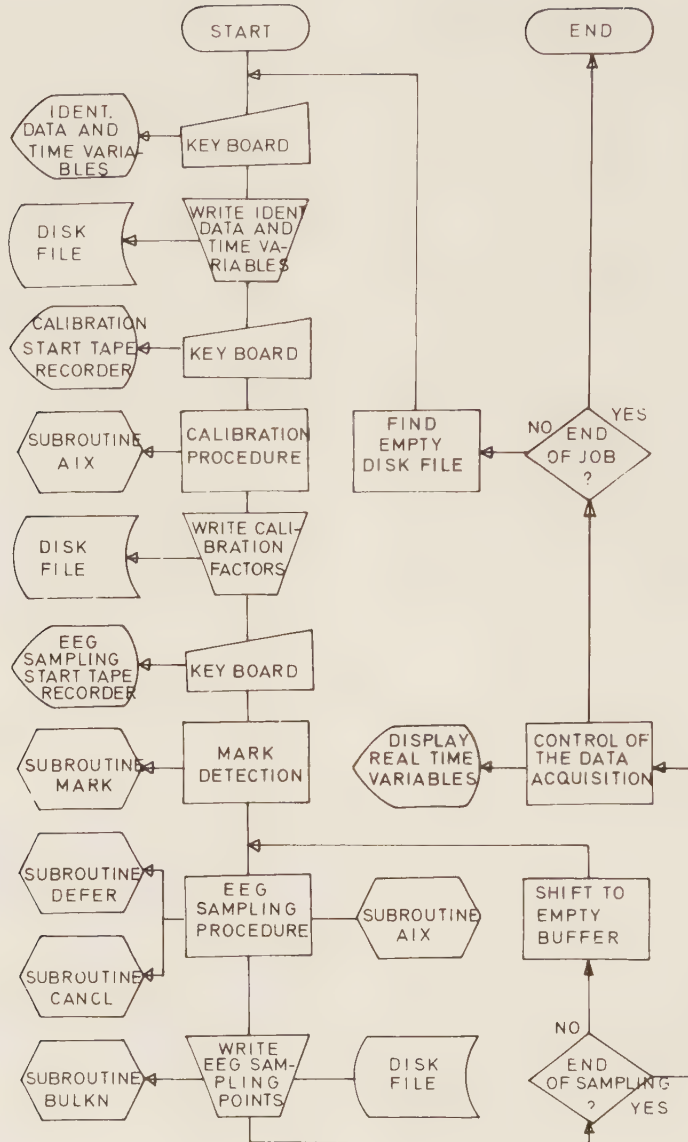


Fig. 5. System flowchart of the EEG data acquisition program.

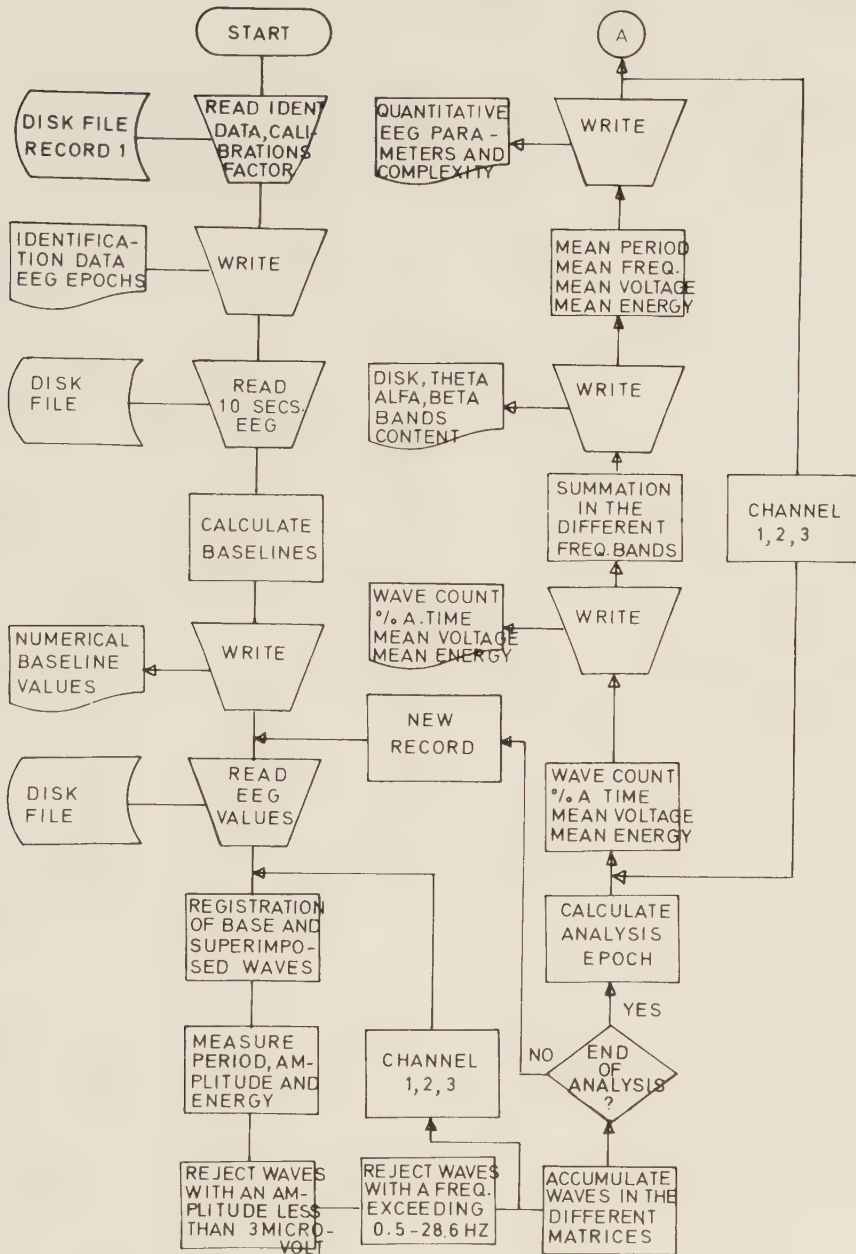


Fig. 6. System flowchart of the EEG analysis program.

LABORATORY OF CLINICAL NEUROPHYSIOLOGY
GENTOFTE HOSPITAL, COPENHAGEN

EEG NO. 27952-2 ANALYSED 10/10 1972

TAPE NO. 5 MARK 1710

CHANNELS 3 2 4

SECTION DELAY SAMPLING
1 0. 100.

CHANNEL 3 ANALYSIS TIME= 98.920

FREQ.BAND	WAVE COUNT	PCT-TIME	MEAN VOLT	RMS/ROOT(HZ)
1	0.000	0.00	0.00	0.00
2	0.000	0.00	0.00	0.00
3	0.000	0.00	0.00	0.00
4	0.020	0.48	23.59	4.22
5	0.030	0.61	33.04	5.27
6	0.050	0.84	27.91	4.06
7	0.151	2.11	26.21	3.52
8	0.515	6.41	29.05	3.65
9	1.556	16.86	34.69	4.11
10	2.294	22.36	34.45	3.85
11	1.940	17.04	28.90	3.05
12	0.576	4.60	30.75	3.12
13	0.596	4.47	25.33	2.49
14	0.535	3.75	25.95	2.46
15	0.525	3.41	22.51	2.06
16	0.454	2.72	21.53	1.89
17	0.657	3.61	20.61	1.74
19	0.707	3.53	20.60	1.66
21	0.404	1.81	17.24	1.32
24	0.515	2.06	14.93	1.08
27	0.707	2.47	11.47	0.78

CHANNEL 3 ANALYSIS TIME= 98.920

FREQ.BAND	WAVE COUNT	PCT-TIME	MEAN VOLT	RMS/ROOT(HZ)
DELTA	0.000	0.00	0.00	0.00
THETA	0.252	4.05	27.16	3.90
ALPHA	6.884	67.29	32.23	3.61
BETA	5.105	27.88	19.89	1.71
TOTAL	12.242	99.23		

AVG.FREQ= 12.336 MEAN VOLT= 26.983 MEAN ENERGY= 2.824

AVG.PERIOD= 0.0810

COMPLEXITY= 0.044

Fig. 8. Printer output from the analysis. Results from one channel only.

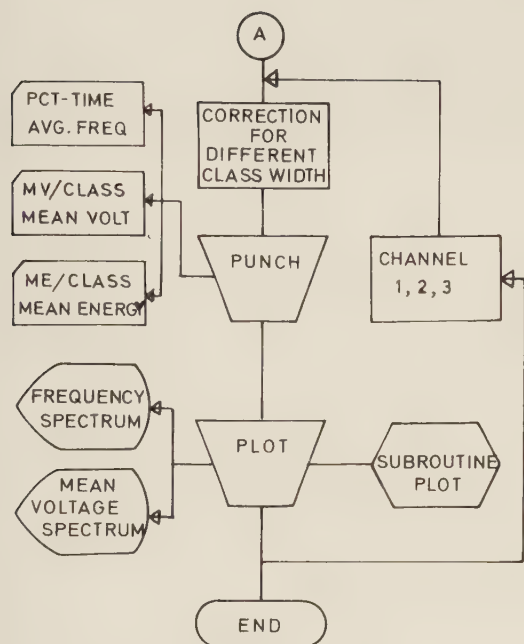


Fig. 7. System flowchart of the EEG analysis program. Continuation of fig. 6.

7. Mode of availability

The source listings of the program are available from the Department for Data Processing in Medicine, Gentofte Hospital, DK-2900 Copenhagen, Denmark on request.

Acknowledgement

The authors wish to thank Mogens Jørgensen M.D., head of the Department for Data Processing in Medicine, Gentofte Hospital for his valuable co-operation and support.

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CHANNEL 3 EEG No. 27952-2

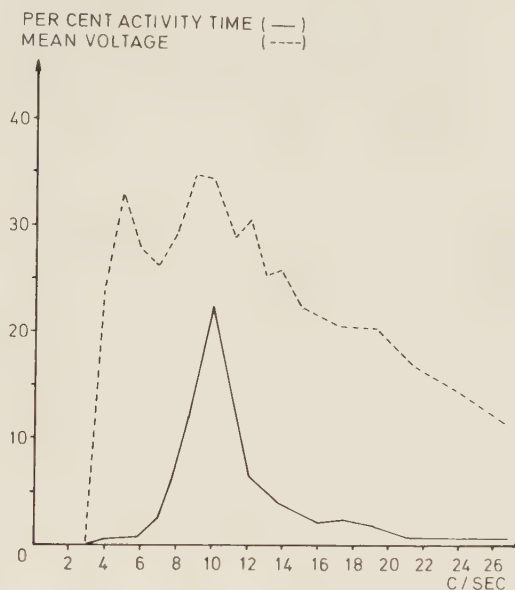


Fig. 9. X-Y plotter output (same data as presented in fig. 8) showing the per cent activity time polygon and the corresponding mean voltage polygon. Abscissa: Frequency in cps, ordinate: Per cent activity time and microvolt respectively.

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HEPATIC ENCEPHALOPATHY EVALUATED BY AUTOMATIC PERIOD ANALYSIS OF THE ELECTROENCEPHALOGRAM DURING LACTULOSE TREATMENT

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Abstract. Eleven patients with liver cirrhosis and operative portacaval shunts have been followed clinically and by automatic period analysis of the EEG to study the effects of lactulose on the cerebral manifestations of liver disease. In three patients disturbances of consciousness of hepatic coma character were relieved, manifested by an increase of the dominant EEG frequency and a shift in the frequency spectrum towards normal. The improvement was evident within two to five days and was maintained for two days after withdrawal. Eight patients with varying degrees of intellectual impairment, but without disturbances of consciousness, did not improve and the EEG analysis was unchanged except in one with a subnormal dominant frequency. Thus patients with hepatic encephalopathy manifested by disturbances of consciousness and reduction in the dominant EEG frequency responded to lactulose therapy.

In 1966 Bircher et al. (2) reported that lactulose improved psychic functions by preventing coma in patients with severe chronic encephalopathy following liver cirrhosis and portal-systemic shunting of blood. Other investigators (4, 5, 6, 13, 17) have similarly observed an action ascribed to alterations in the production of cerebrotoxic substances and their distribution between large bowel and blood (1, 7). Recently the cerebral metabolic oxygen consumption rate was found to increase from subnormal to normal levels in patients with encephalopathy when treated with lactulose (6). Clinical data and EEG findings, however, were not recorded.

EEG abnormalities have been found to be well correlated with grades of neuropsychiatric disturbances preceding hepatic coma (9), and in

three patients with severe encephalopathy and reduced dominant frequency of the EEG Rorsman and Sulg (11) found that clinical improvement was paralleled by an increase of the dominant EEG frequency. Such an increase may precede clinical improvement by 48 hours (5).

To define more clearly the indications for lactulose treatment we studied EEGs by automatic period analysis in 11 patients with liver cirrhosis and operative portacaval shunts under periodic treatment with lactulose.

MATERIAL AND METHODS

Eleven patients (Table I) were given lactulose (Duphalac® syrup 50% w/w, 66% w/v), 80–120 ml per os per day (Table II), as required to obtain two or three soft motions daily.

In a pilot study patient 1 was followed over a period of two months (Fig. 1). Eight patients were studied for four weeks: twice before treatment and twice during treatment at an interval of four to five days, and finally nine days after discontinuation. In two patients (nos. 10 and 11) control and treatment periods were reversed, because lactulose therapy had been instituted some time before the study began. Each patient acted as his own control.

All studies were made between 10.30 and 11.30 a.m., and outpatients were instructed not to take sedatives or sleeping tablets. Other medical prescriptions were taken as usual. The patients had breakfasted two or three hours before study and all were on normal diet.

Clinical evaluation was made with reference to daily practice of normal skills, to occupation, and to changes in general condition and sleep patterns (Table II).

Arterial blood ammonia measurement was done in connection with EEG examinations in patients 2–10 using the microdiffusion spectrophotometry method of Brown et al. (3). Analyses of the sample, a blind and a standard, were made in triplicate. The coefficient of variation was 5.2%, normal range 40–125 $\mu\text{mol/l}$.

Part of this work was presented at the 4th World Congress of Gastroenterology, July 1970, Copenhagen.

Table I. Laboratory data from 11 patients with liver cirrhosis treated with lactulose (Duphalac®)

Figures within parentheses are normal values

Pat. no.	Sex	Age (y.)	Months after portacaval operation	Serum bilirubin (mg/100 ml) (<1.3)	P & P time (> 65)	Alkaline phosphatases (KA units) (<13)	Serum albumin (g/100 ml) (> 3.7)	Serum γ -globulin (g/100 ml) (<1.3)
1	♂	56	68	1.3	33	22	3.7	1.8
2	♂	55	8	1.2	39	13	3.0	1.4
3	♂	59	9	1.5	41	12	3.6	1.9
4	♀	55	38	1.1	81	31	3.7	2.0
5	♂	50	29	1.3	51	11	3.3	1.8
6	♀	63	26	3.9	71	39	3.7	1.2
7	♀	66	24	1.4	52	9	4.0	1.9
8	♂	42	36	1.5	66	2	4.2	0.9
9	♀	77	11	1.7	30	11	4.2	1.1
10	♀	64	19	0.6	65	10	3.2	1.1
11	♀	65	4	3.9	64	15	3.7	1.0

Electroencephalography

EEG traces were run for 30 min on awake patients with closed eyes (Fig. 2). Signals from the right frontocentral and parieto-occipital leads were pre-amplified (time constant 0.3 sec, low-pass filter 30 c/sec) and recorded on magnetic tape (E. Kaiser's Laboratory, Copenhagen).

Table II. Intellectual impairment, arterial ammonia concentration, and lactulose (Duphalac®) dosage in 11 patients with liver cirrhosis

Pat. no.	Degree of intellectual impairment ^a		Arterial ammonia concentration (μ mol/l) ^b		Lactulose dosage (ml $\times$ 2)
	With-out treat-ment	During treat-ment	Without treatment	During treatment	
1	4/coma	3	—	—	60
2	3	3	103/143/102	133/213	40
3	0	0	98/171/96	80	60
4	0	0	84/54/100	93/138	60
5	2	2	83/85	113/126	60
6	3	3	108/146/134	156/123	30 ^c
7	3	3	72/120/74	33/77	60
8	2	2	78/73/74	82/74	60
9	4	3	134/71/81	101/135	40
10	3	3	114/181	81/31/164	40
11	Coma	4	—	—	60
Mean			103	108	

^a 0 = No complaints or signs of intellectual impairment. 1 = Slight complaints or signs of intellectual disturbance with unaltered working capacity. 2 = Grade 1 with reduced working capacity. 3 = Moderate degree of mental disturbance with working incapacity. 4 = Severely disabling mental disturbance, including disorientation.

^b Blood samples taken at the same time as EEG recordings.
^c ml $\times$ 4.

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Both leads gave almost identical results and therefore only those from the parieto-occipital lead are presented.

Period analysis was made of the first 100-sec section of the EEG trace without artefacts on a small, general purpose digital computer (IBM 1800), using a complex of data programs described elsewhere (14). The programs combine wave detection by peak-to-peak analysis and baseline crossings.

The frequency range of 0.5–28.6 c/sec was divided into 21 frequency classes and the percentage activity time was calculated for each class (Figs. 2 and 3).

The dominant frequency was calculated as the mean value of the five consecutive classes with the greatest total percentage activity time. The frequency distributions were compared using Spearman's rank correlation coefficient (r_s) (12). If two frequency distributions are equal $r_s = 1.0$. Comparisons were made in each of nine patients (nos. 2–10) of EFGs in non-treatment periods, and r_s lay between 0.88 and 0.99, which reflects a spontaneous variation in the EEG spectra.

Criteria for acceptance of change in the EEG related to treatment were that there should be a clear increase in the dominant frequency and that the change in the frequency distribution should be reflected by r_s values below 0.88.

RESULTS

Clinical

Eight patients did not respond to treatment (Table II). Particularly they did not impair following withdrawal of lactulose. Two patients without previous cerebral signs or symptoms of encephalopathy were included only for the EEG studies.

In three patients a clinical improvement was observed within two to five days after the beginning of treatment, and withdrawal of the drug was followed by clinical deterioration (see Case Reports).

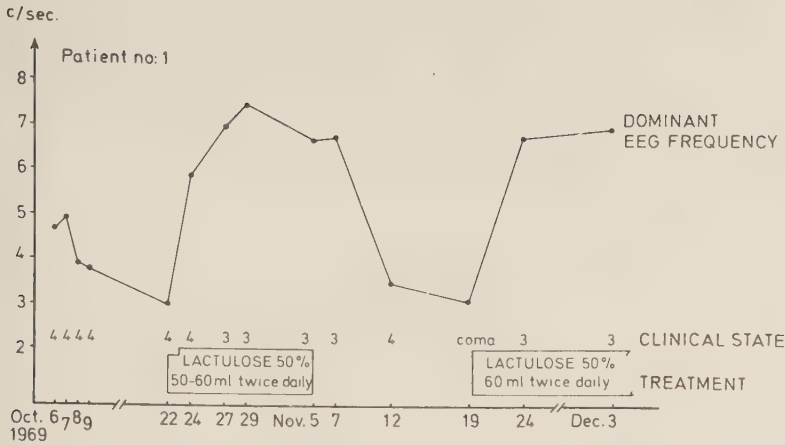


Fig. 1. Relationship between lactulose treatment, clinical state, and the dominant EEG frequency in patient I.

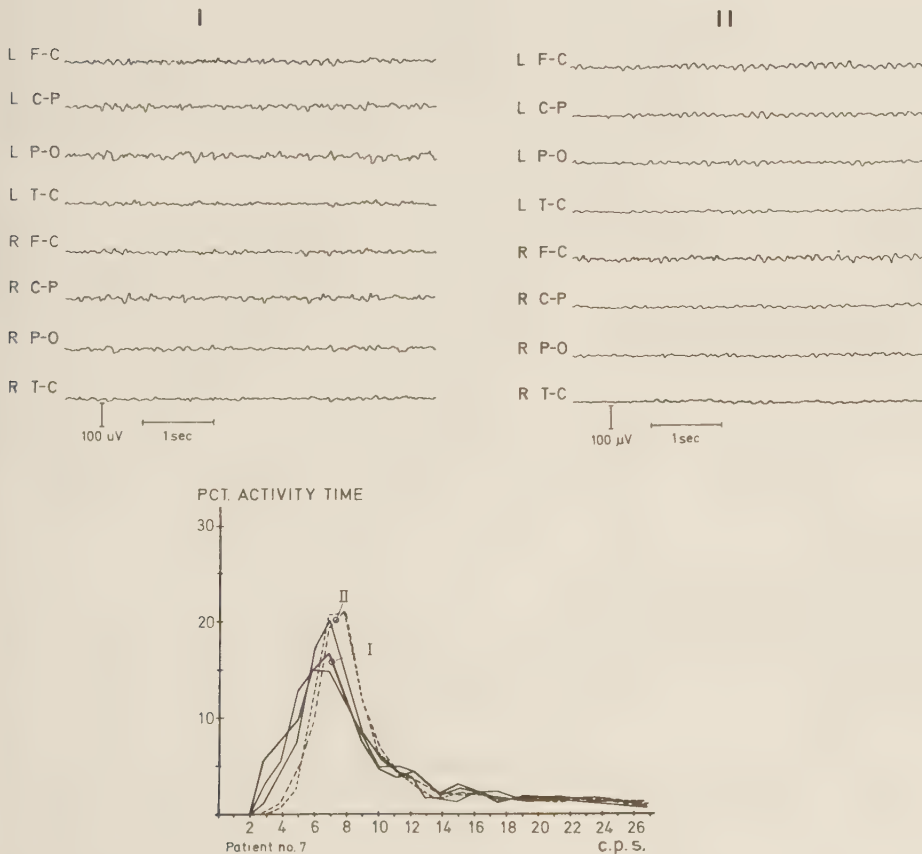


Fig. 2. EEG before (I) and during (II) treatment with lactulose, and the EEG spectra (from 100 sec recordings)

from all 5 examinations of patient 7. Spectra from the EEG traces shown above are encircled.

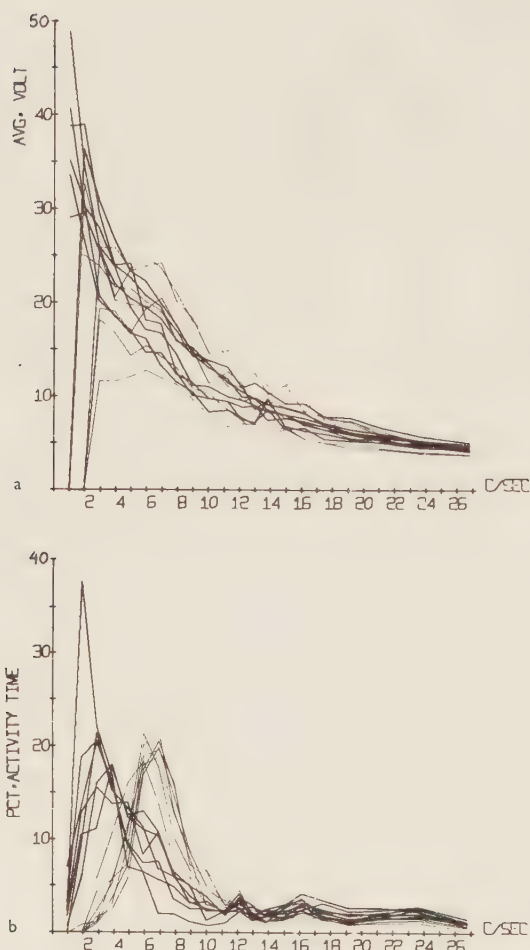


Fig. 3. The average amplitudes in μV (a) and the percentage activity time (b) as functions of frequency in the 14 EEG examinations of patient 1. Thin lines, during treatment; thick lines, control examinations.

Electroencephalography

The EEGs of four patients (nos. 1, 7, 9, and 11) improved. There was a shift to the right in the frequency spectrum (Fig. 3) and the dominant frequency increased, tending to the normal (Fig. 4). In patient 7 these changes were not paralleled by clinical improvement (Fig. 2).

There were no changes in the fast activity above 13 c/sec and no relevant changes in the amplitude/period relation (Figs. 2 and 3). When the dominant frequency was above the lower limit of α -range (7.5 c/sec), it did not alter during treatment (Fig. 4).

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Study of the two patients already under lactulose treatment was begun by interrupting the treatment. No change was apparent in one patient (no. 10), whose dominant frequency was normal. The other (no. 11) deteriorated rapidly and had a reduced dominant frequency (6–7 c/sec) even during treatment.

Blood tests

In contrast with the findings in other studies (2, 4, 17) blood ammonium was not affected by lactulose treatment (Table II, $p > 0.1$, Wilcoxon rank sum test), but patients were not fasting when the blood samples were drawn.

Side-effects of treatment

All patients complained of flatulence and a few of intestinal colic, but these symptoms disappeared after three to four days of treatment. Diarrhoea was frequently a problem but was controlled by reduction of lactulose dosage. One patient rejected treatment after three days because of flatulence and is not included in the study. A further patient (no. 3) discontinued treatment after the first

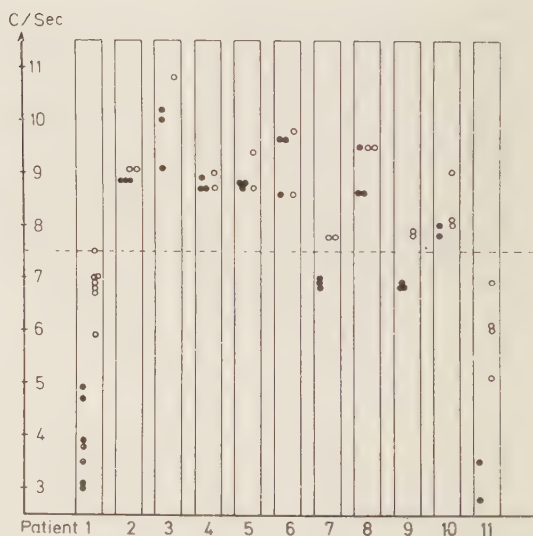


Fig. 4. Dominant frequency from the right parieto-occipital lead in 11 patients with liver cirrhosis. O, Dominant frequency during treatment; ●, control examinations. The lower limit of the α -range at 7.5 c/sec (---) separates the dominant frequencies of the control curves in 4 responders (nos. 1, 7, 9, 11) from those of the non-responding patients.

examination during treatment. One patient under long-term treatment (no. 1), who had had a partial gastrectomy, complained of dumping symptoms when the lactulose dose was above 30 ml.

CASE REPORTS

Case 1 (Figs. 1 and 3)

A 56-year-old man precomatous for some months before treatment, unable to read more than newspaper headlines, markedly slow cerebration and partial disorientation. After two days' treatment he could look after himself, and after a week he could read books, although obvious signs of intellectual impairment remained. Two days after cessation of treatment he had severe disturbances of consciousness, did not respond when spoken to, and had asterixis. One week after resuming treatment his condition and the EEG findings were as during the initial period of treatment and remained stable after 18 months' continued treatment apart from some slight progression of intellectual impairment. He had had two transient periods of confusion associated with sedative drug and alcohol consumption.

Case 9

A 77-year-old woman. Admission to a nursing home thought necessary because of frequent periods of confusion. She complained of fatigue and appeared sluggish. During ten days of treatment she became more awake and active, her memory improved. Nine days after cessation of treatment her condition had returned to the pretreatment level. Treatment was then reinstituted and the response was as before. She has been stable with no episodes of precoma or coma for one year. She lives alone and is able to look after herself.

Case 11

A 65-year-old woman. Lactulose had been given for the preceding four months following portacaval shunt operation. Treatment was interrupted to expose possible indications for continuation. During treatment she required help with personal hygiene, had marked intellectual impairment—was not able to understand or reproduce a printed text, which she could however read. Two days after discontinuation of treatment her consciousness was severely disturbed. She was without reaction to the environment. Five days after resuming treat-

ment her condition was as during the initial treatment, but thereafter deteriorated slowly. For a period lactulose was therefore supplemented with and then substituted by neomycin/bacitracin, 2 g of each daily per os. There was no improvement and treatment was changed back to lactulose. She died eight months later with progressive hepatic insufficiency and encephalomyelopathy. A post-mortem was not performed.

DISCUSSION

After portacaval shunt operations in patients with cirrhosis of the liver the dominant EEG frequency is often found to fall to or below the lower limit of α -range (8–13 c/sec) (8, 10). This finding is usually ascribed to an increased action of cerebrotoxic material bypassing the liver through the shunt.

All of the patients in this series had operative portal-systemic shunts, but in none of the patients with dominant EEG frequencies above 7.5 c/sec was any change seen attributable to treatment. This may indicate that liver detoxification in such patients is adequate despite the shunt. Nevertheless, routine liver function tests did not distinguish these patients from those responding to treatment (Table I, $p > 0.1$, Wilcoxon rank sum test).

Three patients with encephalopathy manifested by disturbances of consciousness had dominant EEG frequencies below 7.5 c/sec. In these patients EEG improvement paralleled clinical improvement; but after coma had been relieved, an obvious intellectual impairment persisted despite prolonged lactulose therapy.

Intellectual disturbances are frequent in patients with chronic liver disease and portal-systemic shunts (8, 16), and it has been shown that they are relatively static following shunt operations, which increase the portal-systemic shunting substantially (8). That the intellectual impairment present in most of our patients was unaffected by lactulose supports the assumption that such symptoms are of a chronic, non-toxic nature ("acquired hepato-cerebral degeneration" (15)), and should be distinguished from the disturbances of consciousness ("liver coma"). Such a distinction may explain the otherwise paradoxical finding of Zeegen et al. (17) that lactulose in their series

was beneficial in the three most severely affected of seven patients with encephalopathy.

In two of our patients benefiting from lactulose, withdrawal precipitated hepatic coma. In both patients the dominant EEG frequency was below the normal range even during treatment. Therefore, when lactulose treatment has been found beneficial, any contemplated withdrawal should be most carefully considered.

The side-effects of lactulose seem to be harmless but may be so unpleasant that treatment is refused or must be discontinued. We find this necessary, as do others, in about one in ten patients.

Controlled studies of lactulose are necessary for the evaluation of any possible protective action against the development or progression of the intellectual impairment so often present in patients with liver cirrhosis and portal-systemic shunts (8, 16), and far more common than the recurrent coma syndrome (8).

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PERIOD-AMPLITUDE ANALYSIS OF THE
ELECTROENCEPHALOGRAM CORRELATED WITH LIVER
FUNCTION IN PATIENTS WITH CIRRHOSIS OF THE LIVER

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In hepatic encephalopathy there is a gradual slowing of the background activity of the electroencephalogram (EEG). In the middle stages, usually when the background rhythms are between 4 and 6 c/sec, there is often also pseudoparoxysmal activity of 2-4 c/sec sharp and slow waves in bilateral bursts with bifrontal emphasis (Bickford and Butt 1955; Silverman 1962). The severity of the EEG alterations correlates fairly well with the severity of the clinical affection (Bickford and Butt 1955; Parsons-Smith *et al.* 1957; Silverman 1962).

Deviations from the normal in the background activity of the EEG are not unusual in liver disease even in patients considered clinically to have no encephalopathy, *e.g.*, 24 out of 56 patients in the series of Parsons-Smith *et al.* (1957). To examine the correlation between alterations of the frequency and amplitude of the EEG and the liver function in awake patients with cirrhosis of the liver, we have studied the EEG by period-amplitude analysis (Stigsby *et al.* 1973), and the liver function determined quantitatively by the galactose

elimination capacity (Tygstrup 1964). The study includes patients with and without surgical portocaval anastomosis.

MATERIAL AND METHODS

The EEG and liver function were studied in 40 patients with cirrhosis of the liver, verified by biopsy. Two patients were excluded from the study because of a low voltage EEG without any central trend of the frequency distribution. Ten patients were studied before and after portocaval anastomosis. Fourteen patients were studied only after the operation, and 14 patients were not operated. Thus, there were 24 studies in patients without and 24 studies in patients with, a surgical shunt. In the shunted patients studies were made from 2 months to 6 years (median 12 months) after the operation. Twenty-five healthy volunteers served as a control group for the EEG examination (Table I).

The EEG and liver function studies were done within 2 weeks and usually 1-3 days apart. The

TABLE I

Age and dominant EEG frequency in patients and normal controls; and correlation coefficients between dominant frequency and galactose elimination capacity (GE) in the patients.

	N	Age*	Dominant* frequency	$\tau_{GE/EEG}$ (Kendall correlation coefficient)	$\tau_{G/EEG, Age}^{**}$
Cirrhosis - shunt	24	54.5 ± 9.9	8.54 ± 1.01	0.38 ($P=0.009$)	0.34 ($P=0.0006$)
Cirrhosis + shunt	24	52.5 ± 9.9	7.79 ± 1.08	0.24 (n.s.)	
Normal controls	25	50.7 ± 7.0	9.23 ± 0.73		0.38 } 0.33 0.18 }

* Mean ± SD.

** Kendall partial correlation coefficient.

patients were awake and responsive and thought to be in their habitual condition. Patients on treatment with neomycin, lactulose, or protein restriction were not considered for the study.

The liver function was determined by the galactose elimination capacity as described by Tygstrup (1964) from the linear slope of the arterial blood concentration after single dose intravenous injection. The normal value for this test is above 350 mg/min.

The EEG was recorded simultaneously on paper and tape with the patients lying supine with their eyes closed. Surface electrodes placed according to the "ten-twenty" system were employed. From the right and left parieto-occipital leads, 100 sec of EEG without artefacts were selected from the first 5 min recorded after a conversation with the patient to check wakefulness. The period-amplitude analysis of the selected EEG epoch was performed on a general purpose digital computer (IBM 1800). By zero-crossing and peak detection the period and amplitude for each single wave were measured. The per cent time and the mean peak-to-peak amplitude were calculated for each of 21 frequency bands covering a frequency range from 0.5 to 28.6 c/sec. For each recording these figures represented an activity and an amplitude distribution. The dominant frequency was calculated as the interhemispheric mean of the modes of the activity distributions. The EEG analysis has been described in detail by Stigsby *et al.* (1973).

The comparison between two patient groups of the activity and amplitude measurements was made for each of the frequency bands. Comparisons were also made for the dominant frequencies between the groups. Non-parametric statistical methods described by Siegel (1956) were used: (1) the Mann-Whitney U-test; (2) the Kendall correlation coefficient ($\tau_{x/y}$); and (3) the Kendall partial correlation coefficient ($\tau_{x/y,z}$). Slightly modified standard computer subroutines were used in the statistical calculations¹.

RESULTS

1. Relation to porto-caval shunting

The EEG activity distribution showed a shift

¹ IBM System/360 Scientific Subroutine Package, Version III, form no. GH20-0205-4, New York 1970.

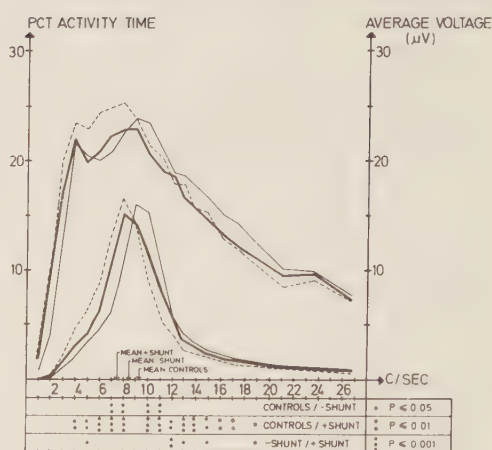


Fig. 1. The mean activity distributions (lower curves) and mean amplitude distributions (upper curves) in EEG recordings from the right parieto-occipital lead in 25 normal controls (thin lines), in 24 patients with cirrhosis of the liver without porto-caval anastomosis (thick lines), and in 24 patients with cirrhosis and porto-caval anastomosis (dotted lines). The means of the dominant EEG frequencies of each group are indicated by arrows. Significant activity differences between the groups are registered at the corresponding frequency bands.

towards lower frequencies when passing from the control subjects to the non-shunted cirrhotics and further to the shunted cirrhotics (Fig. 1). This was reflected by significant differences of the per cent time in some of the frequency bands, as marked at the bottom of Fig. 1. The alpha activity was decreased at 10–12 c/sec, it was overlapping at 9 c/sec, and increased at 8 c/sec in the patients compared with the control subjects, and the amount of theta activity was increased in patients with a surgical shunt.

The frequency shift was also reflected by a reduction of the dominant frequency (Table I). The age of the non-shunted patients was slightly higher than the age of the shunted patients and control subjects (Table I), but no correlation was found between age and the dominant frequency of the EEG, for which reason this age difference was disregarded.

Ten patients studied both before and after porto-caval anastomosis underwent a change in the dominant frequency between the studies ranging from -1.8 c/sec to $+0.6$ c/sec. The median change was -0.65 c/sec ($P \leq 0.025$). No difference was found between the dominant EEG frequency of patients studied more than a year

and patients studied less than a year after portocaval shunt surgery.

In both patient groups and in the control group the mean amplitude was greatest (20–25 μ V) corresponding to the dominant frequency. This was seen in the individual curves as well as in the average curves of the groups (Fig. 1). Due to the shift towards lower frequencies in the shunted patients the mean amplitudes at 6 and 7 c/sec were increased ($P \leq 0.05$) compared with the control subjects. This was the only difference between the groups observed in the amplitude data.

There were slightly reduced amounts of beta activity in the activity distributions of the patients (Fig. 1), and only randomly recorded activity in the delta range. On visual inspection no pseudo-paroxysmal activity was found.

2. Relation to liver function

In the combined studies of shunted and non-shunted patients, as well as in the non-shunted patients alone, there was a statistically significant positive correlation between the galactose elimination capacity and the dominant EEG frequency. In the shunted cirrhotics alone the correlation was not significant. The correlation was independent of age, as shown by the equal size of the Kendall correlation coefficient and partial correlation coefficient (Table I).

DISCUSSION

Our findings indicate that both liver function and porto-systemic shunting are of importance for the slowing of the EEG in some patients with cirrhosis of the liver. However, both the dispersion of data and the overlap between observations in normal subjects and patients were great. Accordingly, the predictive value of EEG analysis with respect to the liver function and *vice versa* is small concerning the awake cirrhotic patient, being restricted to a possible association of a galactose elimination capacity of less than 225 mg/min in non-shunted patients with a subnormal dominant EEG frequency (Fig. 2). The decrease in the dominant frequency following portocaval shunt surgery is in keeping with observations reported by Read *et al.* (1968), who also found that a preoperative dominant frequency

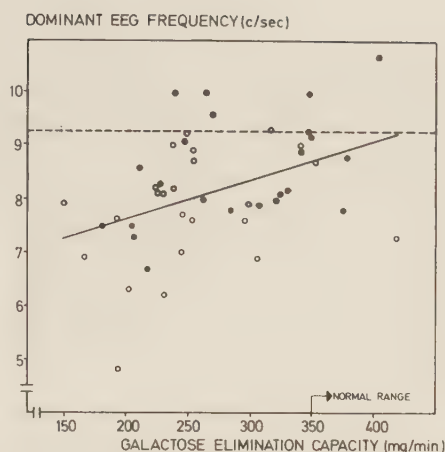


Fig. 2. The relation between the dominant EEG frequency and the galactose elimination capacity in patients with cirrhosis without porto-caval anastomosis (filled circles) and patients with porto-caval anastomosis (open circles). The regression line is calculated by the least square method. The dotted line and the shaded area represent the mean dominant frequency ± 2 standard deviations of the EEGs from the 25 control subjects.

below 7 c/sec seemed to be a warning against postoperative hepatic encephalopathy. Our results suggest that an impaired metabolic liver function could be the underlying factor responsible for this.

The amount of toxic material produced in the bowel is included with the liver dysfunction and porto-systemic shunting among the pathogenetic factors causing hepatic encephalopathy (Sherlock *et al.* 1954). Its influence on the EEG is known from studies which have shown slowing of the EEG in some cirrhotics following protein loading, and normalization following the administration of neomycin, lactulose or low protein diet (Parsons-Smith *et al.* 1957; Rorsman and Sulg 1970; Kardel *et al.* 1972; Hawkes *et al.* 1973). The influence of the liver function and the porto-systemic shunt on the EEG may be that the large shunt leads to increased toxic load to the systemic circulation and hence to the brain, and the impaired liver function leads to delayed detoxication. That a number of patients with large surgical shunts had no slowing of the EEG may be due to variations of the brain tolerance, and to variations in the amount of toxic material produced in the bowel. Unfortunately, it is hardly possible to account for either of these two factors in a

quantitative way. In order to keep variation low in the production of toxic bowel material, patients on continuous treatment with neomycin, lactulose or protein restriction were not included in this study, as it was not thought safe to withdraw such treatment for the purpose of the study (Kardel *et al.* 1972). But since patients known to benefit from such treatment usually have a low dominant EEG frequency (Kardel *et al.* 1972; Hawkes *et al.* 1973), and a low galactose elimination capacity (Kardel 1974), their exclusion may have reduced the slope of the regression line of Fig. 2.

Results quite similar to those presented here were obtained in patients with chronic renal failure. Hagstam (1971) found a shift towards lower frequencies in the EEGs of uraemic patients and a significant correlation between the degree of azotaemia and the mean frequency of the EEG. This emphasizes the fact that slowing of the EEG in patients with cirrhosis of the liver is an unspecific expression of metabolic disturbance of the brain.

Measurements of the amplitudes and activities in the upper frequency bands provided little useful information.

SUMMARY

Studies of the activity distribution of the EEG by period-amplitude analysis were made in 40 patients with cirrhosis of the liver, with or without a surgical porto-caval anastomosis, and in 25 control subjects. One hundred seconds of EEG from the two parieto-occipital leads were examined.

A quantitative determination of the liver function was made in the patients by the galactose elimination capacity.

There was gradual slowing of the EEG when passing from the control subjects to non-shunted cirrhotics and shunted cirrhotics. This was reflected by significant differences of the amount of activity in some of the frequency bands and by a decrease of the dominant EEG frequency. Amplitude measurements yielded little useful information.

There was a statistically significant, although weak, positive correlation between the dominant EEG frequency and the galactose elimination

capacity in the non-shunted patients and in both patient groups considered together, while the correlation was not significant in the shunted patients alone.

RESUME

ANALYSE AMPLITUDE-PERIODE DE L'EEG, EN RELATION AVEC LA FONCTION HEPATIQUE, CHEZ DES PATIENTS AVEC CIRRHOSE DU FOIE

Cette étude constitue une analyse de l'EEG en termes de fréquence et d'amplitude chez 40 patients avec cirrhose du foie, ayant ou non subi une anastomose portocave; 25 sujets normaux servirent de témoins. Cent secondes de tracé EEG pris à partir de deux électrodes pariéto-occipitales, ont été utilisées. La fonction hépatique était estimée quantitativement chez les patients par la capacité d'élimination du galactose.

Un ralentissement progressif de l'EEG a été observé lorsqu'on passait des sujets normaux aux cirrhotiques sans shunt, puis à ceux avec shunt; il se manifestait par une différence significative de la proportion d'activité dans certaines fréquences et par une diminution de la valeur de la fréquence EEG dominante. En revanche les évaluations d'amplitude n'ont apporté que peu de renseignements utilisables.

Une corrélation positive statistiquement significative (mais faible) a pu être établie entre la fréquence EEG dominante et la capacité d'élimination du galactose, chez les patients non porteurs de shunt et dans les deux groupes de patients pris globalement; en revanche, la corrélation n'a pas été significative chez les patients porteurs de shunt pris isolément.

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ELECTROENCEPHALOGRAPHIC CHANGES IN THE DOMINANT HEMISPHERE DURING MEMORIZING AND REASONING

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The effect of mental activity on the electroencephalographic (EEG) background activity has been intensely studied since Berger (1930, 1931) drew attention to a possible relationship. Mundy-Castle (1957) reviewed previous findings and presented his own results indicating augmented theta and beta activity during mental arithmetic, but no clearcut relationship between alpha rhythm and mental activity. Since then quantitative methods for EEG analysis have been applied (Cooper and Mundy-Castle 1960; Walter et al. 1967; Elul 1969, 1972; Lopes da Silva and Storm van Leeuwen 1969; Lehmann 1971; Ishihara and Yoshii 1972). Most of these studies have been explorative in nature and almost exclusively dealing with the alpha rhythm.

The findings concerning changes in the alpha rhythm during different mental activities seem ambiguous. A number of studies suggest that alpha activity and alpha amplitude are decreased during mental arithmetic (Glass 1964, 1968, 1970; Pollen and Trachtenberg 1972; Rosadini and Ferrillo 1972; Dolce and Waldier 1974). Conversely, Mulholland and Runnals (1962) and Mulholland (1972, 1973) found that increased attention led to increased occurrence of alpha activity, and increased alpha amplitude was found by Kreitman and Shaw (1965) during performance of different psychometric tasks and mental arithmetic. With open eyes, both decreased and increased alpha activity during performance of mental tasks have been observed (Grünwald et al. 1968, 1972; Creutz-

feldt et al. 1969; Legewie et al. 1969; Klinger et al. 1973), as well as no change of EEG activity at all (Surwillo 1971). Only a few authors have studied the effects of mentation upon the frequency spectrum of the EEG in different hemispheric regions, e.g., Giannitrapani (1970, 1971), who found a global decrease of alpha activity simultaneously with an increased amount of beta activity in the temporal and prefrontal areas during various mental activities, including mental arithmetic.

In the present study we attempted to find regional electrophysiological correlates to the increase of cerebral blood flow in localized regions of the dominant hemisphere during psychological testing (Ingvar and Risberg 1967; Risberg and Ingvar 1968, 1973). With slight modifications we have used the same types of test and experimental design as described by Risberg and Ingvar (1973). The EEG was recorded from some of the cortical regions which showed a flow increase during performance of the tests.

Material and Methods

The EEG was recorded in eighteen healthy volunteers during four experimental conditions, including rest and performance of psychometric tests. The order of presentation of the experimental conditions was randomized. Instructions about the tests were given immediately before each measurement period, which lasted for about 15 min.

(1) Auditory memory test

In an auditory memory test, involving short-term memory, the test problem was to detect a sequence of three consecutive odd numbers. One digit random numbers were recorded on tape with one digit each second. Each time three consecutive odd numbers were read in the earphone a marking pulse was also read from a second tape channel and recorded on the EEG machine for later control of the performance. The subjects were lying supine with their eyes closed. When the subjects detected a sequence of three odd numbers they pressed a button. This elicited a pulse which was recorded on the EEG machine. Only EEG sections with simultaneous marking pulses, i.e. correct detection of numbers, were selected for analysis.

(2) Auditory rest

The EEG was also recorded during an 'auditory rest' control condition while the subjects were listening to white noise with closed eyes. EEG sections for analysis were selected from parts of the record where the EMG from the extrinsic laryngeal muscles, an unspecific measure of wakefulness (Berger 1961), had approximately the same amplitude as during the auditory test.

(3) Visual reasoning test

A reasoning test with 30 items, each consisting of five geometric figures (Thurstone 1938; Dureman and Salde 1959), was employed. The figures were projected on a white screen placed on the wall so that minimal movements of the head and eyes were required. Four of the five geometric figures had a common feature. The subjects were asked to find the figure which differed from the others. The answer was given by pressing the button the number of times corresponding to the chosen figure. The replay pulses were recorded on the EEG machine. Each item was presented to the subjects until they

answered, but no longer than one minute. Only EEG sections with correct answers were included in the analysis.

(4) Visual rest

A control EEG recording for the visual reasoning test was made with the subjects lying supine looking at a dot on the screen with about the same light intensity as the test figures. This enabled the subjects to fixate the gaze. EEG sections were analyzed from periods with an EMG amplitude of the external laryngeal muscles about equal to that during the visual test.

Eight subjects were excluded because one or more of the EEG channels was contaminated with extracerebral electrical activity (mainly EMG and eye movement potentials, detected with electrodes placed periorbitally). From the remaining ten right-handed subjects (seven females and three males, 19–30 years of age, mean 25.0 years) 50 sec of artefact-free EEG from both rest and test performances were selected for analysis in accordance with the above criteria. The sample was chosen following the first minute of the test period to permit possible EEG changes to manifest themselves, in accordance with the observation that a change in the regional cerebral blood flow starts within the first minute of the performance of the psychological test (Risberg and Ingvar 1972). It was impossible to select completely artefact-free sections of two EEGs during the two visual conditions, due to low voltage muscle potentials in the frontal region. However, the amounts of extracerebral activity were almost equal in the test and in the rest recordings.

The analysis epoch was set at 50 sec, as a longer epoch does not improve the results of period-amplitude analysis of a normal EEG (Stigsby, in preparation). Three channels of EEG were recorded from the dominant hemisphere (determined by conventional methods for handedness) by surface electrodes placed 'anterior' and 'posterior' to the electrode marks F_3 (or F_4), T_3 (or T_4), and O_1 (or O_2)

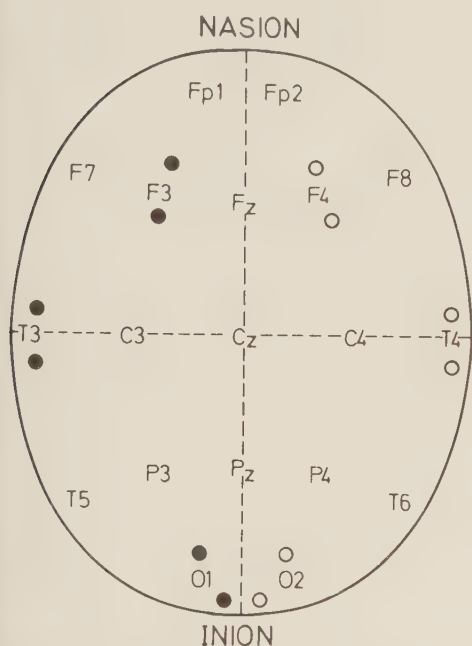


Fig. 1. The surface electrodes were placed 1 cm 'anterior' and 'posterior' respectively to the electrode marks F₃ (or F₄), T₃ (or T₄) and O₁ (or O₂). Filled circles correspond to right-handed, open circles to left-handed subjects.

(abbreviations in accordance with the international 'ten-twenty' system (Jasper 1958)) (Fig. 1). Bipolar leads with an electrode distance of 2 cm were used in order to measure from as small a cortical area as possible. This increased the recording difficulties as the signal/noise ratio decreased because of the small EEG amplitudes.

The EEG was recorded on a 16 channel EEG machine (band-pass 0.5–70 c/sec) connected to (1) an on-line automatic EEG analyser (Hjorth 1970) and (2) an analog tape recorder (Hewlett-Packard). All EEGs were analysed on-line and recorded on tape for later automatic period-amplitude (P-A) analysis. The automatic analyser yields three quantitative EEG parameters: (1) *power*, i.e. a measure of the mean power (amplitude variance), (2) *frequency*, i.e. a measure of the mean frequency

(the ratio between the standard deviation of the slope and the standard deviation of the amplitude) and (3) *complexity*, i.e. a measure of the frequency spread (the slope spread in standard deviations per unit time) (Hjorth 1970, 1973). The parameters called activity and mobility by Hjorth (1970) are identical to the terms power and frequency, which are used here in order to avoid confusion with the P-A terminology. Output from the P-A analysis consisted of the per cent activity time (%AT) and the mean voltage (MV) in 21 frequency bands covering the range from 0.5–28.6 c/sec, besides the mean period frequency (MPF) and the mean voltage of the analysis epoch (MVA). Methodological and procedural details concerning the P-A analysis have been described by Stigsby et al. (1973).

The calculated EEG parameters were arranged in a two-fold matrix, and a column analysis was performed using the Wilcoxon Signed Rank Test for matched pairs (Siegel 1956, Wilcoxon and Wilcox 1964). This analysis yielded information about the statistical significance of the change within each single EEG parameter. With the purpose of testing for differences between EEG changes during the auditory and visual tests as well as between the three cortical regions, the percentage differences (test minus rest) of the EEG parameters were compared, using the same statistics. The level of statistical significance was preset to 0.05. The data processing was carried out on a general purpose digital computer (IBM 1800).

Results

I Differences between the test and rest conditions

The results are presented in Table I and Fig. 2. Table I shows the results of the P-A analysis accumulated in the frequency bands delta, theta, alpha and beta, the MPF, the MVA and the three parameters from the automatic analyser. Fig. 2 shows the mean activity

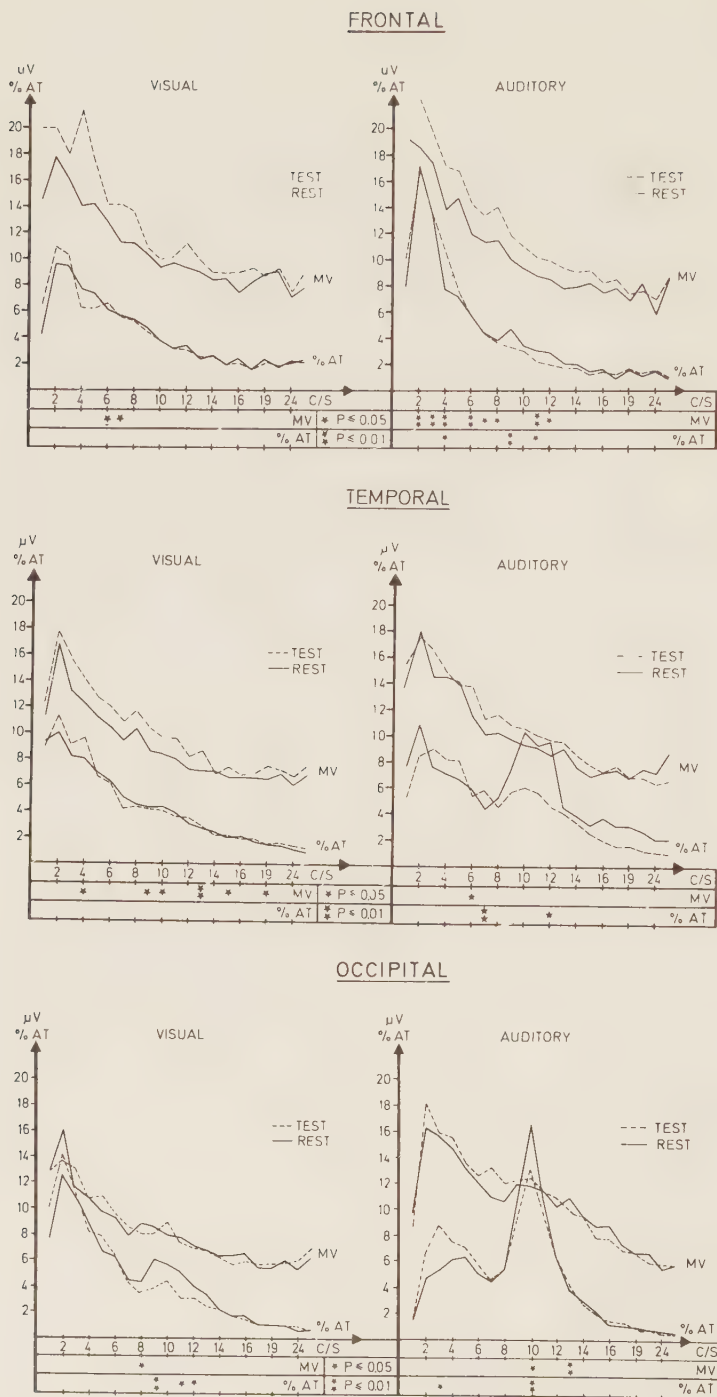


Fig. 2. The mean activity distributions (the 2 lower curves in each system of co-ordinates) and mean voltage distributions (the 2 upper curves in each system of co-ordinates) in EEGs from the frontal, temporal and occipital regions of the dominant hemisphere in 10 normal subjects. The dotted lines correspond to the test, the solid lines to the rest conditions. Significant differences between the test and rest conditions are indicated by asterisks at the corresponding frequency bands.

and mean amplitude distributions of the EEGs from the three cortical regions during the two test/rest situations.

1. Auditory memory test

(a) *Frontal region.* P-A analysis: the alpha activity decreased while the %AT in one band (4 c/sec) increased significantly (Fig. 2). There was no difference in the MPF. There was an increase of amplitude in the delta, theta and alpha frequency bands, and the MVA was increased (Table I). Automatic analysis: an increase of the parameter power was seen, while there were no differences in the parameters frequency and complexity (Table I).

(b) *Temporal region.* P-A analysis: an increase of the %AT in the 7 c/sec and a decrease in the 12 c/sec frequency bands were seen (Fig. 2). The decrease of alpha activity was not significant. An increase of amplitude in the 6 c/sec frequency band was seen. There were no differences in the parameters MPF and MVA. Automatic analysis: no changes of the parameters were observed.

(c) *Occipital region.* P-A analysis: an increase of the activity in the 3 c/sec and a decrease in the 10 c/sec frequency bands were seen (Fig. 2). The alpha activity was decreased, but the change was not significant. The MV in the 10 c/sec frequency band increased, while there was a decrease in the MV of the beta frequency band (Table I). There were no differences in the parameters MPF and MVA. Automatic analysis: no changes of the parameters were observed.

2. Visual reasoning test

(a) *Frontal region.* P-A analysis: only the increase of the MV in the theta frequency band was statistically significant (Table I and Fig. 2). No differences were found in the %AT data or in the parameters MPF and MVA. Automatic analysis: the parameter power increased, while there were no changes in the frequency and complexity.

(b) *Temporal region.* P-A analysis: there was an increase of the MV in single frequen-

cies within the theta, alpha and beta bands (Fig. 2), but only the MV of the alpha frequency band showed a consistent increase (Table I). The MVA increased whereas no differences in the %AT of the MPF were observed (Table I). Automatic analysis: the parameter power increased, while the other two parameters showed no change.

(c) *Occipital region.* P-A analysis: a decrease of the %AT in the alpha frequency band was the most marked change (Table I and Fig. 2). In addition, the MV of the 8 c/sec frequency band decreased significantly. There were no differences of the parameters MPF and MVA. Automatic analysis: the parameter frequency showed a significant decrease during the test (Table I), while the other two parameters showed no change.

II Differences between the visual reasoning and auditory memory tests

(a) *Frontal region.* Except for the %AT in the 5 c/sec frequency band there were no statistically significant differences between the EEG parameter changes of the two tests.

(b) *Temporal region.* The %AT changes in the 7 and 12 c/sec frequency bands differed significantly ($P < 0.02$), and the increase of MVA during the visual test was significantly greater ($P < 0.01$) than during the auditory test. This was especially seen in the beta frequency band.

(c) *Occipital region.* The %AT decrease in the alpha frequency band during the visual test was more pronounced than that during the auditory test ($P < 0.01$), whereas the patterns of change of the MV did not differ in the two tests.

III Differences between the cortical regions

(a) *Auditory memory test.* The MV increase in the alpha frequency band in the frontal region differed significantly ($P < 0.01$) from the MV changes in the occipital region, and a tendency to a more pronounced increase of MV in the frontal region compared

TABLE I

The mean values of the per cent activity time (%AT) and the mean voltage (MV) accumulated in delta, theta, alpha and beta frequency bands, the mean period frequency (MPF), the mean voltage of the analysis epoch (MVA) and the three parameters of the automatic analysis. The percentage changes between the rest and the test conditions and the obtained levels of statistical significance are indicated.

	EEG parameters	Visual reasoning test				Auditory memory test			
		Rest mean	Test mean	Per cent change	P	Rest mean	Test mean	Per cent change	P
Frontal	delta %AT	23.0	27.5		n.s.	38.1	39.4		n.s.
	theta %AT	26.1	24.3		n.s.	24.8	28.0		n.s.
	alpha %AT	20.8	19.8		n.s.	18.5	15.4	-17	0.05
	beta %AT	30.0	29.8		n.s.	21.5	22.1		n.s.
	delta MV	16.9	19.4		n.s.	18.6	21.5	+16	0.01
	theta MV	13.0	16.3	+25	0.05	13.0	15.6	+20	0.001
	alpha MV	10.0	11.1		n.s.	9.7	11.3	+16	0.004
	beta MV	8.1	8.8		n.s.	7.7	8.0		n.s.
	MPF	10.2	9.9		n.s.	8.1	8.0		n.s.
	MVA	9.7	11.0		n.s.	10.2	11.3	+11	0.04
	power / frequency	4	6	+50	0.05	6	10	+66	0.01
	complexity	11.3	9.9		n.s.	8.6	8.0		n.s.
Temporal		222	224		n.s.	210	207		n.s.
	delta %AT	27.3	29.1		n.s.	25.9	22.6		n.s.
	theta %AT	25.9	26.4		n.s.	23.9	27.2		n.s.

alpha %AT	21.0	20.3	n.s.	35.0	27.9	n.s.
beta %AT	24.7	27.0	n.s.	32.0	27.6	n.s.
delta MV	15.1	17.1	n.s.	17.0	17.2	n.s.
theta MV	10.7	12.4	n.s.	12.7	13.3	n.s.
alpha MV	8.4	9.9	0.04	9.3	10.5	n.s.
beta MV	6.8	7.4	n.s.	8.0	7.3	n.s.
MPF	9.0	9.1	n.s.	9.9	9.6	n.s.
MVA	8.4	9.4	0.04	9.5	9.6	n.s.
power	3	5	0.05	4	5	n.s.
frequency	9.8	9.6	n.s.	9.4	9.8	n.s.
complexity	207	202	n.s.	128	125	n.s.
Occipital						
delta %AT	30.8	35.2	n.s.	11.6	16.9	n.s.
theta %AT	25.8	26.6	n.s.	21.8	24.6	n.s.
alpha %AT	26.2	18.6	0.01	51.9	46.0	n.s.
beta %AT	19.5	19.8	n.s.	20.0	20.0	n.s.
delta MV	13.3	13.8	n.s.	16.1	16.8	n.s.
theta MV	9.5	10.1	n.s.	12.6	13.5	n.s.
alpha MV	8.1	8.0	n.s.	11.6	12.0	n.s.
beta MV	6.1	6.3	n.s.	7.6	7.3	0.02
MPF	8.2	7.8	n.s.	9.9	9.4	n.s.
MVA	7.9	8.1	n.s.	10.5	10.8	n.s.
power	4	5	n.s.	7	8	n.s.
frequency	8.2	7.2	0.04	9.8	9.3	n.s.
complexity	180	200	n.s.	179	177	n.s.

to the temporal was seen. The patterns of change of the %AT did not differ in the three regions.

(b) *Visual reasoning test.* The decrease of alpha activity was more pronounced in the occipital region than in either the frontal or temporal region ($P < 0.02$ and $P < 0.05$ respectively). The MV increase in the alpha frequency band in the temporal region was significantly different from amplitude changes in the occipital region ($P < 0.05$), whereas there was no difference in the pattern of change of the %AT or the MV between the frontal and the temporal regions.

Discussion

Numerous studies have shown correlations between the mean frequency of the EEG and other measures of brain activity. In spite of certain exceptions, e.g. during sleep, there is substantial support for the view that the EEG frequency has some relationship to cerebral oxidative metabolism (Obrist 1963; Ingvar et al. 1976) as well as to the cerebral blood flow (Sulg 1969). Little is, however, known about the significance of the EEG amplitude. The mean voltage of the EEG — other things being equal — must be evaluated at a fixed frequency in order to avoid interference with the normal reciprocal relation between frequency and amplitude in the EEG. Evaluated in this way a higher mean voltage signifies more electrical energy in the EEG waves. The EEG amplitude must therefore to some extent reflect fluctuations of the cortical activity of the brain.

By means of two different methods of EEG analysis the present investigation showed that mental activity caused changes in the EEG. Moreover, different forms of mental activity were reflected in different regional EEG patterns and, furthermore, one form of mental activity caused different changes in the frontal, temporal and occipital regions of the dominant hemisphere.

During the auditory memory test increases

of the parameter power and of the EEG mean voltage, caused by increased amplitudes in the delta, theta and alpha frequency bands, were seen in the frontal region. During the visual reasoning test, on the contrary, increases of the power and of the mean voltage, caused by increased amplitude of the alpha frequency band, were seen in the temporal region, as well as slight increases of the mean voltage of the theta frequency band and of the power in the frontal region. In addition to this, a tendency for alpha activity decrease in all three regions was seen during the auditory memory test, whereas this tendency was seen only in the occipital region during the visual reasoning test.

By the experimental design we tried to eliminate probable EEG differences caused by visual or auditory stimulation and perception. Since no speech, reading or writing was necessary during the performance and only very little motor work was needed, we find it arguable that these EEG changes are specific in the sense that they reflect electrical events in certain areas of the cerebral cortex elicited by the particular mental activity. These specific changes appeared in general as increased EEG amplitudes, most often in the theta and alpha frequency bands.

The tendency to a global decrease of alpha activity during the auditory memory test, which was also a vigilance test, should, we feel, be interpreted as a classical alpha blocking phenomenon (Giannitrapani 1971).

The EEG changes in the frontal region during both types of mental activity agree with the generally accepted notion that the frontal association cortex plays a decisive role in mental activity (Luria 1966, 1973). Furthermore, Risberg and Ingvar (1973) demonstrated a regional increase of blood flow in this area of the dominant hemisphere during performance of mental tasks.

No explanation for the EEG changes seen in the temporal region during the visual reasoning test can be given at present. A relation between the present EEG changes and those of the cerebral blood flow recorded in this

region during mental effort appears absent; only small flow changes were found there during reasoning (Risberg and Ingvar 1973). The EEG changes could possibly be caused by activation of the temporo-occipital association cortex, known to be involved in organization of visual perception (Mishkin 1972). They may also reflect participation of temporal structures in reasoning and memory processes (Penfield 1959). It is known that part of the temporal lobe is involved in visual pattern discrimination (Mishkin and Pribram 1954; Pribram and Barry 1956).

The EEG changes in the temporal and occipital regions during the auditory and visual tests respectively were discrete, probably because the experimental design particularly aimed to eliminate EEG changes in the auditory and visual primary cortex.

Summary

The EEG was recorded with bipolar technique in ten normal subjects in the frontal, temporal and occipital regions of the dominant hemisphere in four situations: (1) during an auditory memory test, (2) during 'auditory rest' (listening to white noise), (3) during a visual reasoning test and (4) during 'visual rest' (watching a black dot on a white screen). Computer analysis of the EEG was made by (a) an on-line automatic EEG analyser yielding measures of mean power, mean frequency and frequency spread (complexity) and (b) an off-line period-amplitude (P-A) analysis, which gave per cent activity time and mean voltage in 21 frequency bands.

As compared to auditory rest the auditory memory test gave an amplitude increase frontally in the alpha, theta, and delta bands. During the visual reasoning test there was in addition an amplitude increase in the alpha band in the temporal region. During the auditory test a tendency to a decrease of the alpha activity was seen in all three regions but this decrease occurred only occipitally during the visual test. The two types of mental activity

thus induced two patterns of regional EEG changes. These showed principal similarities to regional cerebral blood flow patterns which have been recorded during visual and auditory tests of about the same types as those used in the present study.

Résumé

Modifications EEG dans l'hémisphère dominant pendant une mémorisation et un jugement

L'EEG a été recueilli en bipolaire chez 10 sujets normaux en frontal, temporal et occipital, sur l'hémisphère dominant, ceci dans quatre situations: (1) test de mémoire auditive; (2) situation de "repos acoustique" (écoute d'un bruit blanc); (3) test d'appréciation visuelle; (4) "repos visuel" (observation d'un point noir sur écran blanc). L'EEG a été traité (a) en ligne, l'analyse automatique fournissant la puissance moyenne, la fréquence moyenne et l'étalement des fréquences et (b) en différé, pour une analyse période-amplitude (P-A), donnant pour 21 bandes de fréquence, le pourcentage de temps d'activité et le voltage moyen.

Par rapport au repos acoustique, le test de mémoire auditive était accompagné d'une augmentation d'amplitude, en frontal, dans les bandes de l'alpha, du thêta et du delta. Pendant le test de jugement visuel, on notait par surcroît une augmentation d'amplitude dans la bande alpha en temporal. Sous test auditif, l'alpha tendait à diminuer partout tandis qu'il ne diminuait qu'en occipital sous test visuel. Ainsi les deux catégories d'activité mentale ont-ils induit deux patterns distincts de modifications régionales de l'EEG. Ces faits en rappellent étroitement d'autres, relatifs aux patterns de débit sanguin cérébral régional, qui ont été observés au cours de tests visuels et auditifs semblables à ceux utilisés dans la présente recherche.

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REGIONAL EEG ANALYSIS AND REGIONAL CEREBRAL BLOOD FLOW IN ALZHEIMER'S AND PICK'S DISEASES

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The EEG abnormalities in *Alzheimer's disease* are well known. They usually begin with a progressive general slowing of the background activity and an increased admixture of delta and theta waves (Letemendia and Pampiglione 1958; Gordon and Sim 1967; Waldton, thesis 1973). However, normal EEGs have been reported in some familial cases confirmed by brain biopsy or autopsy (Feldman et al. 1963), as well as in a few non-verified cases (Rosenstock 1970; Krankenhagen and Köhler 1973). In contrast, the EEG in *Pick's disease* has often been found to be normal or nearly normal, even in advanced stages of dementia (Swain 1959; Nevin 1967).

The cerebral blood flow and the cerebral oxygen uptake are decreased in both Alzheimer's and Pick's diseases (Ingvar and Gustafson 1970; Obrist et al. 1970; Simard et al. 1971; Gustafson and Risberg 1979; Risberg 1980). However, in early stages of Alzheimer's disease a normal cerebral blood flow has been reported (O'Brien and Mallett 1970; Hachinski et al. 1975).

The reduction of cerebral blood flow correlates with the degree of mental deterioration (Ingvar and Gustafson 1970; Obrist et al. 1970; Gustafson and Risberg 1974; Hagberg and Ingvar 1976). Similarly, a significant correlation between the EEG abnormality and the se-

verity of cognitive reduction in Alzheimer's disease has been reported (Jóhannesson et al. 1979), but no association was found between EEG abnormality and duration of the illness (Gordon and Sim 1967). However, in some rather early cases of Alzheimer's disease, Gordon (1968) found progressive EEG deterioration during an observation period of one to four years. A slow EEG deterioration during the course of the disease was also noted by Jóhannesson et al. (1977).

In the present study, the EEG in neuropathologically verified cases of Alzheimer's and Pick's diseases was analysed quantitatively and related to the regional cerebral blood flow (rCBF) measured with the intra-arterial $^{133}\text{Xenon}$ clearance technique. An age-matched group of healthy volunteers served as control for the EEG analysis. All studies were carried out at rest, i.e. with the patients awake and conscious, but as far as possible undisturbed by sensory stimulation.

Material and Methods

Four patients with Pick's disease (2 females and 2 males) were examined at a median age of 57 years (range 49-66 years) and 9 patients with Alzheimer's disease (6 females and 3 males) at a median age of 61 years (range 53-70 years).

The mean age at death was 60 years (range 51-71 years) for the Pick patients, and 65 years (range 58-74 years) for the Alzheimer patients. Thus, the interval between examination and death was about the same for the two groups (3.5 years (range 2-5 years) for the Pick patients and 3.8 years (range 2-7 years) for the Alzheimer patients). The duration of disease ranged from 8-12 years. At the time of the rCBF and EEG examination all patients showed severe intellectual deterioration with memory disturbances and marked reduction of cognitive abilities. The intellectual reduction was less pronounced in the Pick than in the Alzheimer patients, despite approximately the same duration of the illness. However, the Pick patients showed more emotional and personality alterations.

The diagnoses were confirmed by autopsy, which included semi-serial whole-brain microscopic sections used for silver staining. A detailed clinical and neuropathological analysis of the patients has been given elsewhere (Brun and Gustafson 1976).

Thirteen healthy volunteers (7 females and 6 males, median age 59 years, range 45-71 years) served as controls for the EEG analysis.

Regional cerebral blood flow was measured in the 4 Pick patients, and in 6 of the 9 Alzheimer patients, by the intra-arterial $^{133}\text{Xenon}$ clearance technique, which in most cases was performed in conjunction with carotid angiography, using 8 or 32 detectors. During the rCBF measurements strict resting conditions were observed with silence in the laboratory. The patients had small pads covering their eyes. The following flow parameters were calculated from the clearance curves: 1) mean cerebral blood flow (f_m), 2) grey matter blood flow (f_g), 3) white matter blood flow (f_w), and 4) the relative weight of the grey matter (w_g) (Lassen and Ingvar 1972). The results of the flow measurements related to the clinical findings have already been de-

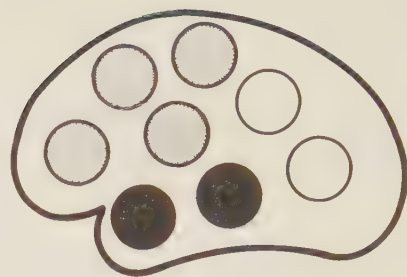


Fig.1: The approximate cerebral localization of the rCBF measurements. The mean flow values of the grey regions were related to EEG parameters of the F3-C3 derivation, the black regions to T3-T5, and the white regions to P3-O1. The ratio between mean flow parameters obtained from grey and white regions constituted the "pre/ post" flow ratio.

scribed (Ingvar and Gustafson 1970; Gustafson and Risberg 1974; Gustafson 1975; Gustafson and Hagberg 1975; Hagberg and Ingvar 1976; Ingvar et al. 1978), as have their relations to the distribution of cortical degenerative changes (Gustafson et al. 1977; Jóhannesson et al. 1977). The rCBF was measured in the left hemisphere, and all flow values were referred to 8 brain regions even in cases where 32 detectors were used (Fig. 1). Pre/postcentral flow ratios ("pre/post" ratio) were obtained by dividing the mean flow parameters of the precentral regions in Fig. 1 by the mean parameters of the postcentral regions.

Measurements of total mean cerebral oxygen uptake based upon mean hemisphere regional blood flow and arterio-venous difference were not carried out (Franzén and Ingvar 1975).

A resting EEG with eyes closed was recorded not more than two days before, or after, the rCBF measurements, using bipolar montages on an 8 or 16 channel EEG machine (band pass 0.5 to 70 Hz). The scalp electrodes were placed according to the international 10-20 electrode system (Jasper 1958). Twenty seconds of artifact free representative resting EEG from the F3-C3, T3-T5 and P3-O1 derivations of the EEG paper trace were digitized by means of a semi-automatic

curve follower (D-MAC pencil follower) connected to a general purpose digital computer (IBM 1800) for later period-amplitude analysis. The analysis epoch of 20 seconds was chosen in accordance with Sulg (1969). By zero-crossing and peak detection the period and amplitude of each single EEG wave were measured. The percentage activity time (%AT) and the mean peak-to-peak voltage (MV) were calculated for each of 21 frequency bands, covering the range from 0.5 to 28.6 Hz. The EEG mean frequency (MF) and the EEG mean voltage of the analysis epoch (MVA) were then calculated. This method of EEG analysis has been described in detail by Stigsby et al. (1973), and the curve follower, its connection to the computer and the computer programs used for the digitizing have also been described (Stigsby and Rasmussen 1970). The vari-

ation due to the semi-automatic digitizing expressed as the standard deviations of the differences between double determinations of MF and MVA was 0.3 Hz and 0.8 μ V, respectively (Stigsby, thesis 1981). To obtain a measure of the pre/postcentral relationship, i.e. the degree of "hyperfrontality" (Ingvar 1979) the ratios between EEG parameters from F3-C3 and P3-O1 ("pre/post" ratio = EEG_{F3-C3}/EEG_{P3-O1}) were calculated.

The results of the EEG analysis in the Alzheimer and the Pick patients were compared with the results from the control group using the Mann-Whitney U test. This was done for the %AT and MV frequency distributions as well as for the MF and the MVA. The relation between EEG and rCBF parameters was tested by the Spearman Rank Correlation Coefficient (Siegel 1956).

TABLE I

EEG mean frequencies (MF (mean $\pm$ SEM) in Hz) and mean voltages (MVA (mean $\pm$ SEM in μ V) in the fronto-central, temporal, and parieto-occipital regions of the left hemisphere of 9 Alzheimer patients, 4 Pick patients and 13 healthy control subjects. Significant differences between the groups are indicated by the obtained level of statistical probability (Mann-Whitney U test).

EEG parameters		Controls n = 13 $\bar{x} \pm$ SEM	Difference Pick – controls	Pick n = 4 $\bar{x} \pm$ SEM	Difference Pick – Alzheimer	Alzheimer n = 9 $\bar{x} \pm$ SEM	Difference Alzheimer controls
MF	(F3-C3)	11.3 $\pm$ 0.60	$P < 0.02$	7.1 $\pm$ 0.24	n.s.	6.7 $\pm$ 0.74	$P < 0.002$
MF	(T3-T5)	11.1 $\pm$ 0.25	$P < 0.002$	6.9 $\pm$ 0.40	n.s.	6.7 $\pm$ 0.62	$P < 0.002$
MF	(P3-O1)	10.5 $\pm$ 0.27	$P < 0.002$	7.6 $\pm$ 0.63	$P < 0.05$	5.2 $\pm$ 0.43	$P < 0.002$
MVA	(F3-C3)	14 $\pm$ 1.2	n.s.	9 $\pm$ 1.1	n.s.	11 $\pm$ 1.2	n.s.
MVA	(T3-T5)	17 $\pm$ 1.2	n.s.	12 $\pm$ 2.8	n.s.	12 $\pm$ 0.8	$P < 0.02$
MVA	(P3-O1)	16 $\pm$ 1.1	n.s.	12 $\pm$ 1.6	n.s.	10 $\pm$ 0.8	$P < 0.002$

Results

Alzheimer patients

The Alzheimer patients showed slowing of the EEG mean frequency and decrease of the mean voltage (Table I). The activity within the delta and theta frequency bands was increased, and decreased within the alpha and beta frequency bands. The mean voltage of the

delta activity was increased, whereas the mean voltage of the alpha activity was decreased as compared to the controls (Fig. 2a). When visually evaluated, all these EEGs were considered as moderately to severely abnormal, with a diffuse slowing and deterioration of the background activity. Additionally short

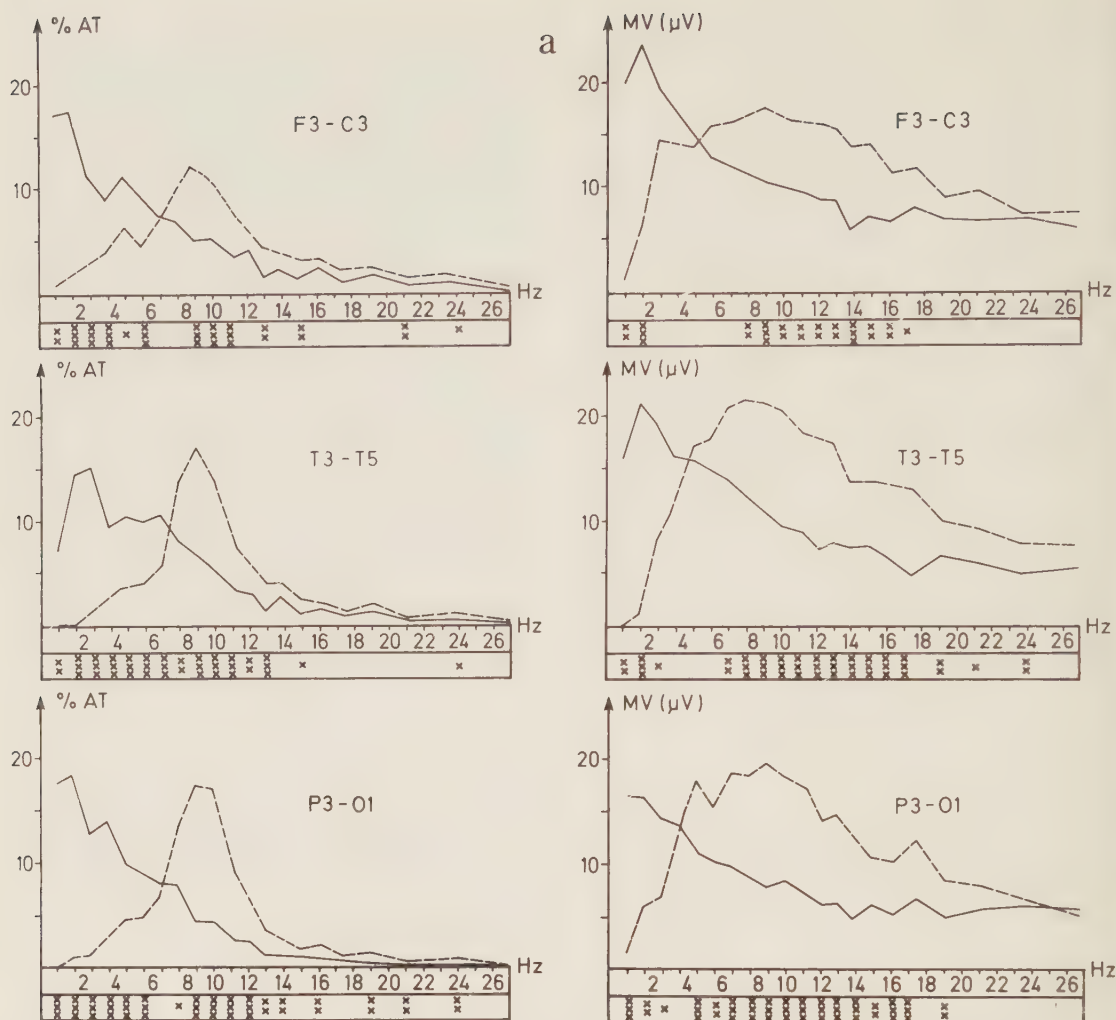


Fig. 2. a and b: The mean activity distributions (left column) and mean voltage distributions (right column) in EEGs from the fronto-central, temporal, and parieto-occipital regions of the left hemisphere in 9 patients with *Alzheimer's disease* (solid curves) (a), in 4 patients with *Pick's disease* (solid curves) (b), and in 13 healthy controls (stippled curves). Significant differences between patients and controls are indicated by asterisks at the corresponding frequency bands (* $p < 0.05$; ** $p < 0.025$; *** $p < 0.002$, Mann-Whitney U test).

trains of bifrontal delta waves of increased amplitude (100-250 μV) were noted in some records.

The mean "pre/post" frequency ratio was 1.30 (SD = 0.33), which implies a significant increase ($p < 0.05$) compared to the controls (1.09, SD = 0.21).

Pick patients

In the 4 Pick patients the EEG mean frequency was also decreased, although

less so than in the Alzheimer patients (Table I). The amount of slow activity was increased, but the alpha activity was well preserved especially in the parieto-occipital region. The mean voltage of the delta activity was increased, whereas the mean voltage of the alpha activity was decreased as compared to the controls (Fig. 2b). On visual evaluation, one of the 4 EEGs was found to be slightly to moderately abnormal due to a periodic

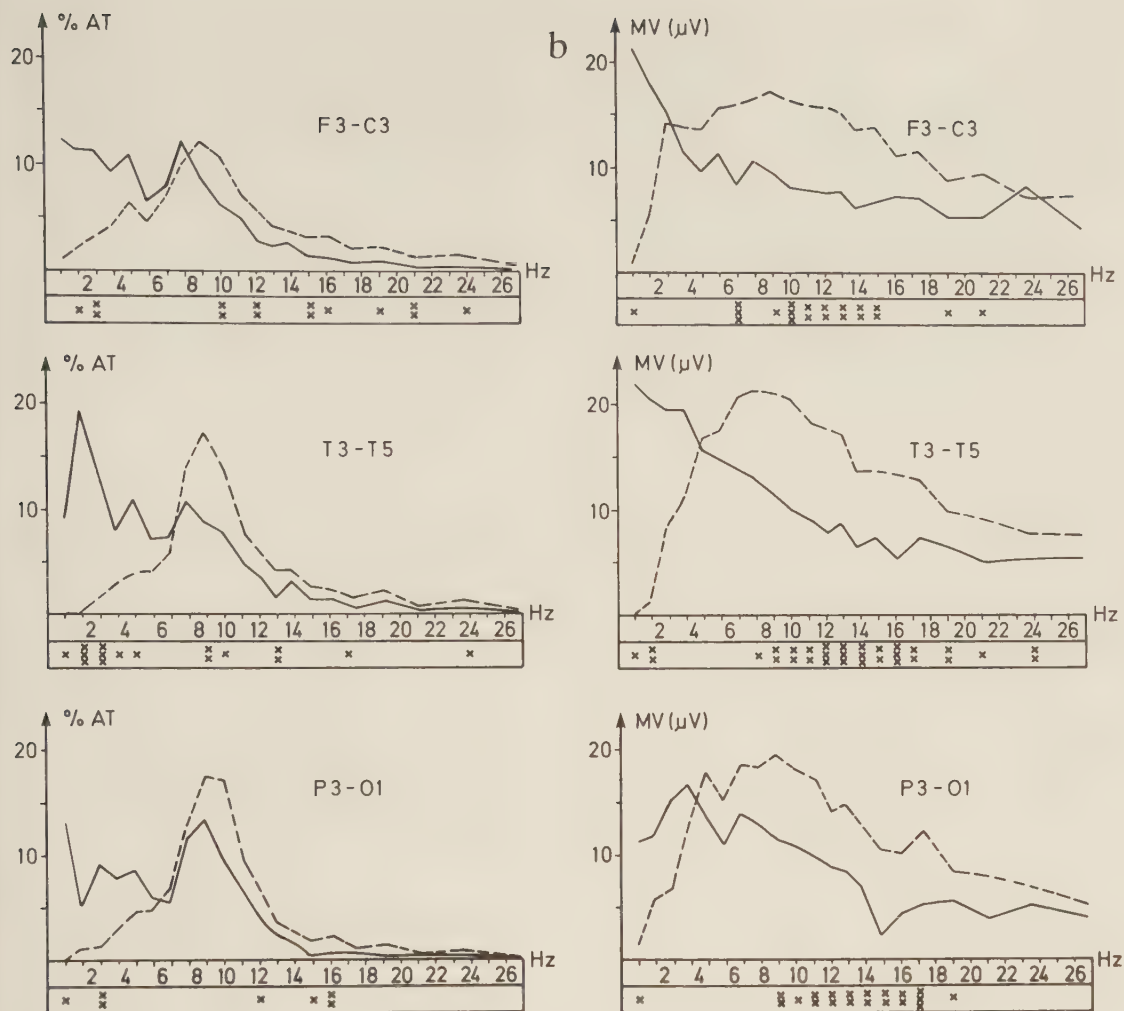


Fig 2b: For legend see fig 2a.

general slowing of the background frequency, whereas the 3 others were considered to be normal. Even when only the three visually normal records were analysed quantitatively, the abnormal frequency pattern described above was confirmed. The mean "pre/post" frequency ratio was 0.96 (SD = 0.17) which was not significantly different from that of the controls.

Pick versus Alzheimer

The MF in the Alzheimer patients was significantly lower than in the Pick patients (Table I). This was mainly due to more delta and theta activity in the Alzheimer group, and more alpha activity in the Pick patients. There was no difference in EEG mean voltage between the two groups. The mean "pre/post" frequency ratio of the Alzheimer patients was significantly higher ($p < 0.05$) than that of the Pick patients.

EEG related to regional cerebral blood flow

In a regional comparison the MF of the Pick patients correlated significantly with the f_g and f_w (Table IIa). Such a correlation was not found in the Alzheimer patients (Table IIb). Taking all patients together, a significant correlation was, however, only found between the MF and the f_w (Table IIc). The association between EEG frequency and blood flow was most prominent in the parieto-

occipital region. Furthermore, the quantity of theta activity and the EEG mean voltage showed a significant negative correlation with the f_g and f_w , again most striking in the Pick patients (Table IIa-c).

The correlation between the "pre/post" EEG frequency ratio and the "pre/post" flow ratio taking all 10 patients together was highly significant, especially regarding the f_g (Table III).

TABLE II

a-c: Spearman Rank Correlation Coefficients indicating the relationship between EEG and rCBF parameters in the fronto-central, temporal, and parieto-occipital regions of the left hemisphere of (a) 4 patients with Pick's disease (number of observations = 12), (b) 6 patients with Alzheimer's disease (number of observations = 18), and (c) Pick and Alzheimer patients taken together (number of observations = 30). The percentage activity time (%AT) accumulated in delta, theta, alpha and beta frequency bands, EEG mean frequency (MF), and EEG mean voltage (MVA) were compared with mean cerebral blood flow (f_m), grey matter flow (f_g), white matter flow (f_w), and the relative weight of the grey matter (w_g).

rCBF parameters	EEG parameters					
	MF	MVA	Delta %AT	Theta %AT	Alpha %AT	Beta %AT
IIa						
f_m	.60 *	-.62 *	-.24	-.25	-.35	.49 *
f_g	.67 **	-.65 *	-.29	-.55 *	-.22	.48
f_w	.64 *	-.59 *	-.12	-.53 *	-.18	.48
w_g	.17	-.54 *	-.01	.09	-.48	.41
IIb						
f_m	.05	-.03	.11	-.34	.02	.25
f_g	-.27	-.14	.38	-.35	-.21	-.14
f_w	.28	-.09	-.28	-.45 *	.18	.24
w_g	.05	-.09	.05	-.24	.03	.19
IIc						
f_m	.27	-.23	-.11	-.36 *	-.06	.32 *
f_g	.09	-.35 *	.04	-.38 *	-.18	.09
f_w	.45 **	-.26	-.33 *	-.54 **	.13	.30
w_g	.11	-.21	-.02	-.15	-.10	.23

* $P < 0.05$; ** $P < 0.01$

TABLE III

Correlation coefficients (Spearman r_s) of pre/postcentral EEG mean frequency (MF) ratio and "pre/post" ratios of mean cerebral blood flow (f_m), grey matter blood flow (f_g), white matter flow (f_w) and relative weight of the grey matter (w_g) in all 10 patients.

EEG parameter	'Pre/post' ratios			
	rCBF parameters			
	f_m	f_g	f_w	w_g
MF	.59 *	.77 ***	.33	.53

* $P < 0.05$

*** $P < 0.001$

Discussion

In this study, the EEG and the regional cerebral blood flow has been investigated for the first time in a quantitative way in autopsy confirmed cases of Alzheimer's and Pick's diseases. The number of patients was rather few, which expresses the difficulty of obtaining material of this type. Two limiting factors in the study should be emphasized; first the study was carried out entirely during resting conditions, and no activation procedures were applied. Second, the cerebral regions in which the rCBF was measured and the EEG recorded were only approximately the same.

In Pick's disease the quantitative EEG analysis showed that the EEG, even when visually interpreted as normal, was clearly different from that of a healthy control group. However, as expected from the visual analysis, the EEG abnormality of the Alzheimer patients was much more pronounced than in the Pick patients, a finding which is in accordance with previous studies (Letemendia and Pampiglione 1958; Swain 1959; Gordon and Sim 1967; Nevin 1967; Jóhannesson et al. 1977). The high pre/postcentral EEG frequency ratio of the Alzheimer

patients also separated them from the Pick patients. This "hyperfrontality" of the EEG (Ingvar 1979; Ingvar et al. 1979) differed clearly from that seen in the controls. The abnormal, but different EEG patterns in Pick's and Alzheimer's diseases are of differential diagnostic importance. They might be used in the diagnosis of organic dementia. Additionally an early correct diagnosis is a prerequisite in treatment trials of Alzheimer's disease (Glen and Whalley 1979; Kendal 1979). Controlled quantitative EEG studies of other types of dementia, and of the reversible dementia-like diseases, are, however, needed before the usefulness of EEG in dementia diagnosis can finally be assessed.

The association between the EEG abnormality and the severity of the disease (Gordon and Sim 1967; Jóhannesson et al. 1979) could not be further elucidated in the present study, because the patients were in an almost equally advanced stage of the disease. Likewise, it was impossible to examine the relation between the duration of the disease and the degree of EEG abnormality, because the scatter of the duration was quite small.

The coupling between EEG frequency, cerebral blood flow, and cerebral metabolic rate for oxygen is well established in animal experiments (Baldy-Moulinier and Ingvar 1968; Freeman and Ingvar 1968) and there is also substantial support for the existence of a similar coupling in man (Sulg 1969; Ingvar et al. 1976), even though there are certain important exceptions, e.g. in children and during sleep. A main question in this study was therefore, whether EEG abnormalities expressed in quantitative values correlate with the regional cerebral blood flow in Alzheimer's and Pick's diseases. Is it then possible, on the basis of EEG findings, to draw any conclusions about the rCBF in these disorders? For the Pick patients this question could be answered positively, because of

consistent significant correlations between EEG and rCBF parameters (Table IIa), whereas in the Alzheimer patients a distinct relationship between EEG and rCBF did not appear. However, the Alzheimer patients also contributed to the significant correlations found on taking all patients together. This was especially striking concerning the pre/postcentral ratio of rCBF and EEG, where the highest correlation between grey matter blood flow and EEG mean frequency was found (Table III). This implies that the interregional EEG relations reflect the interregional blood flow distribution in both types of dementia. The negative, although not statistically significant correlation between EEG frequency and the grey matter blood flow in the Alzheimer patients (Table IIb) was at variance with our primary assumption of a direct relationship between EEG frequency and rCBF. The precentral flow decrease in the Alzheimer patients was less pronounced and the postcentral flow decrease more pronounced than the EEG mean frequency indicated. However, this did not interfere with the highly significant correlation between pre/postcentral EEG frequency and rCBF ratios found in all patients, and was very much in agreement with the "hyperfrontal" flow distribution found in the Alzheimer patients, i.e. a high relative flow precentrally, and a low relative flow postcentrally, in spite of a reduced mean hemisphere blood flow (Ingvar et al. 1978). These CBF findings correlated with the predominant temporo-parieto-occipital cortical degeneration found in the Alzheimer patients (Brun and Gustafson 1976).

A possible explanation for the consistent correlations between EEG and rCBF in the Pick but not in the Alzheimer patients, could be a defective autoregulation in Alzheimer's disease, resulting in an uncoupling between rCBF and oxidative metabolism, the latter known to be closely associated with the EEG (Obrist et al. 1963; Ingvar et al. 1976).

That an impaired autoregulation could be present in demented patients was indicated, but not proven, by the direct correlation between systemic blood pressure and cerebral blood flow recorded by Hedlund et al. (1964). However, in similar demented patients, Simard et al. (1971) found an intact autoregulation. A number of conditions are known to interrupt the cerebral autoregulation, e.g. hypoxia (Freeman and Ingvar 1968) in agreement with which there is no correlation between EEG and rCBF in cerebral infarction (Mosmans, thesis 1974; Kogure et al. 1980); acute hypertension (Strandgaard 1978); chronic alcoholism in some instances (Jóhannesson et al. 1980); and in experimental animals, increased "cerebral sensitivity to ammonia" along with portal systemic shunting (Gjedde et al. 1978). The existence of chronic cerebral hypoxia in Alzheimer's disease is, however, not likely. None of the other conditions mentioned was known to be present. The findings could, however, also be explained by a different pathology in the two disease. Brainstem structures of importance for the regulation of the EEG activity are more often involved in Alzheimer's than in Pick's disease. The blood flow in the brainstem or the deeper brain structures was not measured by the present method. Therefore, the influence of EEG changes caused by brainstem dysfunction could not be taken into account. However, it should be mentioned that a diffuse rCBF reduction without corresponding gross loss of cortical neurones can also be found with severe brainstem lesions (Ingvar et al. 1964; Ingvar and Sourander 1970; Gustafson et al. 1977).

Another explanation for the dissociation between EEG and rCBF could be that of a different influence of the abnormal central cholinergic system in Alzheimer's disease (Davies and Maloney 1976; Perry et al. 1977, 1978; Smith and Swash 1978). The selective loss of cholinergic neurones (Bowen et al. 1977, 1979) could explain the reduction of

CBF but hardly the EEG abnormalities, because as also pointed out by Roth (1979) "dead cells tell no tales". However, the reduced acetylcholine synthesis without concomitant changes in the overall glucose metabolism (Sims et al. 1980) could be the reason for the EEG abnormality, as anticholinergic drugs produce an EEG dominated by diffuse delta and theta activity without alteration of consciousness (Longo 1966). Direct correlation studies must be performed to establish the overall coupling between EEG frequency, blood flow and metabolism. This is now possible by means of positron emission tomography which measures regional cerebral metabolism non-invasively in man, not only in the cerebral cortex, but also in deep brain structures.

Summary

The EEG in 9 Alzheimer and in 4 Pick patients, all confirmed at autopsy were studied. In all Pick patients, and in 6 of the 9 Alzheimer patients, the regional cerebral blood flow (rCBF) was measured in the left hemisphere, using the intra-arterial $^{133}\text{Xenon}$ clearance technique. Three EEG leads (F3-C3, T3-T5 and P3-O1) were analysed by means of computer. The EEGs from 13 healthy volunteers matched for age served as controls.

The Alzheimer patients showed slowing of the EEG mean frequency in all regions, with increased delta and theta, and decreased alpha and beta. In contrast, the alpha was preserved parieto-occipitally in the Pick patients, who also showed delta and theta increase, although less so than the Alzheimer patients. The ratio between the mean frequency of the fronto-central and the parieto-occipital regions was increased in the Alzheimer and slightly, but insignificantly decreased in the Pick patients. The EEG in Pick's disease, which is usually considered to be relatively nor-

mal even in advanced stages of dementia, was thus clearly different from that of healthy controls.

In the Pick patients the regional EEG mean frequency correlated significantly with the corresponding regional flow values. This was not so in the Alzheimer patients indicating different pathophysiology in the two disorders. In all patients the EEG mean frequency correlated significantly with the white matter blood flow. Also the quantity of theta activity and the EEG mean voltage showed significant negative correlations with the regional grey and white matter blood flow, again most striking in the Pick patients.

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ELECTROENCEPHALOGRAPHIC FINDINGS DURING MANTRA MEDITATION (TRANSCENDENTAL MEDITATION). A CONTROLLED, QUANTITATIVE STUDY OF EXPERIENCED MEDITATORS

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Based on analysis of EEG, heart rate, galvanic skin resistance and oxygen consumption, Wallace (1970) and Wallace et al. (1971) postulated that transcendental meditation (TM) induces a wakeful hypometabolic state different from an ordinary relaxed drowsy state. The main EEG changes seen during TM were increased regularity and amplitude of the alpha activity. Supporting Wallace's proposal, Banquet (1973) concluded, on the basis of spectral analysis of the EEG, that the meditative state was a unique state of consciousness, separate from wakefulness, drowsiness or sleep.

This assumed hypometabolic state is, however, not restricted to TM, as subjects who had learned a relaxing method were also able to decrease their oxygen consumption significantly more by relaxing than by just sitting with the eyes closed (Beary et al. 1974). Further, Fenwick et al. (1977) concluded that both the metabolic changes and the EEG phenomena during TM could be explained by accepted physiological mechanisms, as the hypometabolic state was not more than that produced by muscle relaxation and the EEG changes were not different from those observed in the state of sleep onset.

Hebert and Lehmann (1977) observed theta bursts with frontal dominance exclusively in subjects practising TM and nearly twice as often during meditation as compared to ordinary wakefulness.

Pagano et al. (1976) reported that a con-

siderable part of the meditation time was spent in various sleep stages. Also Wachsmuth (Thesis 1978) noticed sleep episodes during TM. The EEG pattern during these episodes could not be differentiated from that seen during sleep onset (Wachsmuth et al. 1980). On the contrary, Tebêcis (1975) did not find any change of EEG activity during TM.

With these ambiguous EEG findings during TM in mind, the present study was undertaken to analyse quantitatively, and controlled, the effect of TM on the EEG. We have compared the EEG recorded during TM with that during various stages of consciousness: wakefulness, drowsiness, sleep onset and sleep. All the meditators had year-long experience and they were used while not meditating as their own controls. Furthermore, we have compared the EEGs from the TM group with those of an age-matched control group not practising TM.

Material and methods

Fourteen healthy subjects (5 females and 9 males, 22–60 years of age, median age 27 years), who had practised TM twice daily for at least 2 years, with the longest TM experience of 8 years, volunteered for the examination. The TM technique introduced by Maharishi Mahesh Yogi is a method to reduce mental activity by means of a simple silent repetition of a sound free of any meaning: a

mantra (Bloomfield et al. 1975). All subjects had their meditation technique checked within 2 months before the examination. None had any neurological disease, nor had any experienced significant head injuries. One subject was rejected from the study because his EEG was contaminated with extracerebral activity, mainly muscle and movement potentials, to such a degree that it made computer EEG analysis impossible. Thirteen healthy volunteers (8 females and 5 males, 21–63 years of age, median age 28 years) who were not practising TM or other types of meditation, zen, yoga, etc., served as controls. Except for two females on oral contraceptives in the control group, none of the participants was treated medically, or had a daily alcohol consumption. No alcohol was taken for at least 24 h before the study.

The EEG was recorded bipolarly with platinum iridium needle electrodes (DISA) placed according to the international 10-20 system during TM and during closed-eyed wakefulness (stage W), drowsiness (stage W-I), sleep onset (stage I) and, in 8 of the 13 subjects, also during sleep (stage II–III). The sleep stages were visually classified according to the EEG pattern (Rechtschaffen and Kales 1968). This visual classification was later confirmed by computer analysis, as the quantitated EEGs during wakefulness, drowsiness, sleep onset and sleep differed significantly one from another. The terms 'wakefulness', 'drowsiness', 'sleep onset' and 'sleep' are used solely for a level of consciousness determined by the EEG. The subjects were divided at random into two groups, A and B. In group A the examination began with meditation followed by sleep, in group B vice versa.

During meditation and closed-eyed wakefulness the subjects sat comfortably in a chair with subdued light in the room. During drowsiness and sleep the subjects lay supine. The EEG was recorded for 5 min before TM, during 20 min of TM and until 5 min after, as well as during a period of up to 1 h when the subjects were trying to fall asleep or slept (8 subjects).

After the EEG recording the subjects completed a questionnaire regarding their subjective experiences of the meditation and the examination situation.

Fifty to 100 sec of EEG without artifacts were selected for analysis 5, 10 and 15 min after TM had started, and during wakefulness, drowsiness, sleep onset and sleep. The following derivations of the EEG were used: F3-C3, T3-T5, P3-O1, F4-C4 and P4-O2. Eye movement potentials were detected by surface electrodes placed periorbitally. The EEG was recorded on a 16-channel EEG machine, bandpass 0.5–70 Hz, connected to an analog tape recorder. The EEG was recorded on tape for later automatic period-amplitude analysis. Output from the period-amplitude analysis was the percentage activity time (% AT) and mean voltage (MV) in 21 frequency bands covering the frequency range from 0.5 to 28.6 Hz. In addition, the mean frequency of the percentage activity time distribution (MF) and the mean voltage of the analysis epoch (MVA) were calculated (Stigsby et al. 1973).

The Wilcoxon Matched-Pairs Signed-Ranks test and the Mann-Whitney U test (Siegel 1956; Wilcoxon and Wilcox 1964) were used for the statistical evaluation.

Results

EEG differences between TM and states of wakefulness, drowsiness and sleep

The EEGs during TM were not different from those recorded during wakefulness and drowsiness, but clearly different from those recorded during sleep onset and sleep (Table I, Fig. 1a–c). The EEG frequency spectra of wakefulness, drowsiness, sleep onset and sleep differed significantly one from another, but constituted a continuum of EEG changes with decreasing alpha and increasing theta and delta activity as the subjects tended to fall asleep (Table I). The frequency spectra during TM were in the same continuum between the stages of wakefulness and drowsiness (Fig. 1a–c).

TABLE I

The EEG mean frequency (MF) and the mean voltage (MVA) (mean $\pm$ S.E.M.) measured fronto-centrally, temporally and parieto-occipitally during wakefulness, drowsiness, sleep onset and sleep. Significant differences between TM and the sleep stages are indicated by the level of statistical probability (* $P < 0.05$; ** $P < 0.01$; Wilcoxon Matched-Pairs Signed-Ranks test).

EEG region	EEG parameter	TM ($\bar{x} \pm$ S.E.M.)	Wakefulness ($\bar{x} \pm$ S.E.M.)	Drowsiness ($\bar{x} \pm$ S.E.M.)	Sleep onset ($\bar{x} \pm$ S.E.M.)	Sleep ($\bar{x} \pm$ S.E.M.)
Fronto-central	MF (c/sec)	9.7 $\pm$ 0.33	10.3 $\pm$ 0.25 *	9.9 $\pm$ 0.35	9.5 $\pm$ 0.41	8.9 $\pm$ 0.38 *
	MVA (μ V)	13 $\pm$ 1.0	12 $\pm$ 0.9	12 $\pm$ 0.7	12 $\pm$ 0.9	12 $\pm$ 0.6
Temporal	MF (c/sec)	9.9 $\pm$ 0.44	9.8 $\pm$ 0.18	9.4 $\pm$ 0.29	8.9 $\pm$ 0.38 *	7.8 $\pm$ 0.24 *
	MVA (μ V)	20 $\pm$ 1.9	18 $\pm$ 1.9	17 $\pm$ 1.4 *	14 $\pm$ 1.3 **	12 $\pm$ 1.0 *
Parieto-occipital	MF (c/sec)	10.2 $\pm$ 0.24	10.0 $\pm$ 0.19	9.6 $\pm$ 0.26 *	8.9 $\pm$ 0.35 **	7.9 $\pm$ 0.31 **
	MVA (μ V)	19 $\pm$ 1.7	20 $\pm$ 2.6	18 $\pm$ 1.9	14 $\pm$ 1.4 *	13 $\pm$ 0.8 *

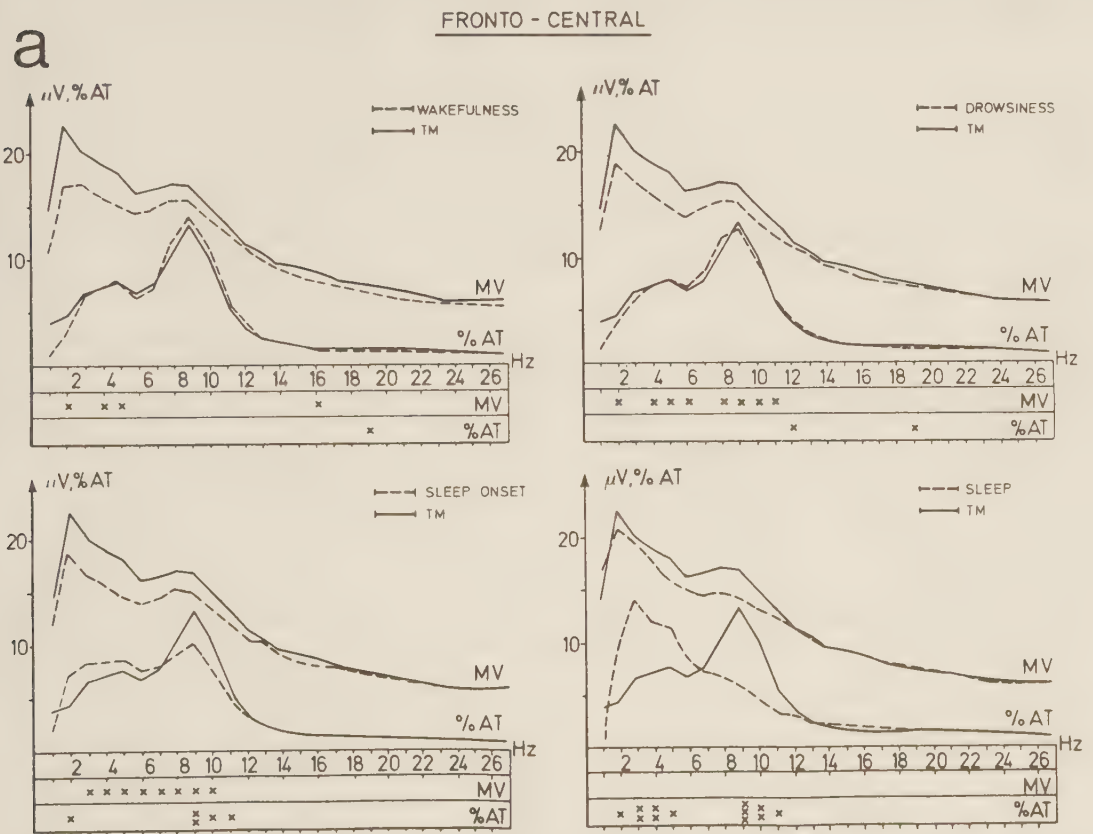


Fig. 1. a-c: the mean activity distributions (% AT) and the mean voltage distributions (MV) in EEGs from the fronto-central (a), temporal (b) and parieto-occipital (c) regions recorded during TM (solid curves), wakefulness, drowsiness, sleep onset and sleep (stippled curves). Significant differences between TM and the 4 stages of consciousness are indicated by asterisks at the corresponding frequency bands (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; Wilcoxon Matched-Pairs Signed-Ranks test).

EEG changes during TM

A slight, but significant slowing of the EEG mean frequency was seen in the left fronto-temporal region during the 20 min of TM, tested after 5, 10 and 15 min of meditation, whereas the mean frequency of the other regions remained stable (Table II). There was no change in the EEG voltage. Fig. 2 shows the individual changes in the EEG mean frequency.

Regional EEG differences during TM

There were no differences between the quantity of EEG activity in the two cerebral hemispheres during TM. The frequency ratio between the fronto-central and the parieto-occipital regions was maintained during TM

and did not change as the meditation progressed.

EEG differences between meditators and controls

The EEG mean frequencies of the TM group during wakefulness were about 1 c/sec lower (Mann-Whitney $U = 16-43$, $0.001 < P < 0.05$) than those of the control group, but still within the alpha range. Also the mean voltages were slightly lower (Mann-Whitney $U = 45$, $P < 0.05$). Fig. 3 shows that the lower EEG mean frequency in the TM group was due partly to more theta activity and partly to a slightly slower alpha frequency in this group, especially in the temporal region.

We found no correlation between the EEG

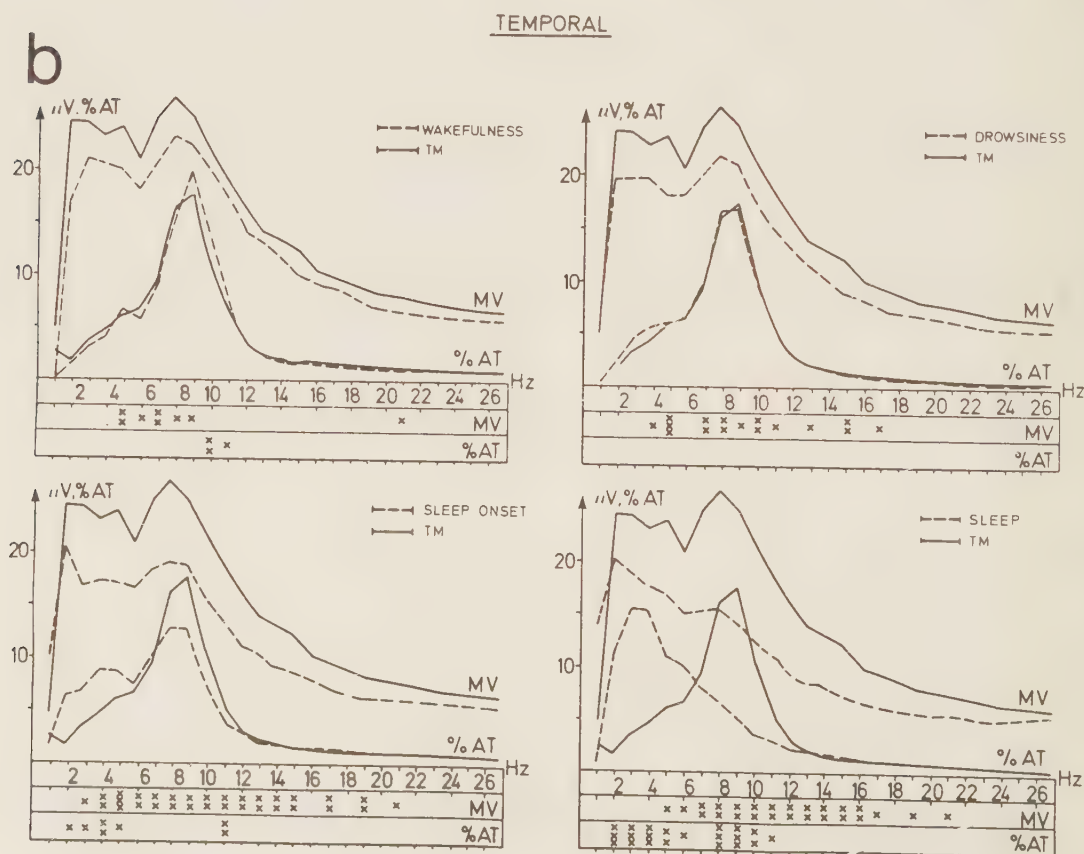


Fig. 1b. For legend see Fig. 1a.

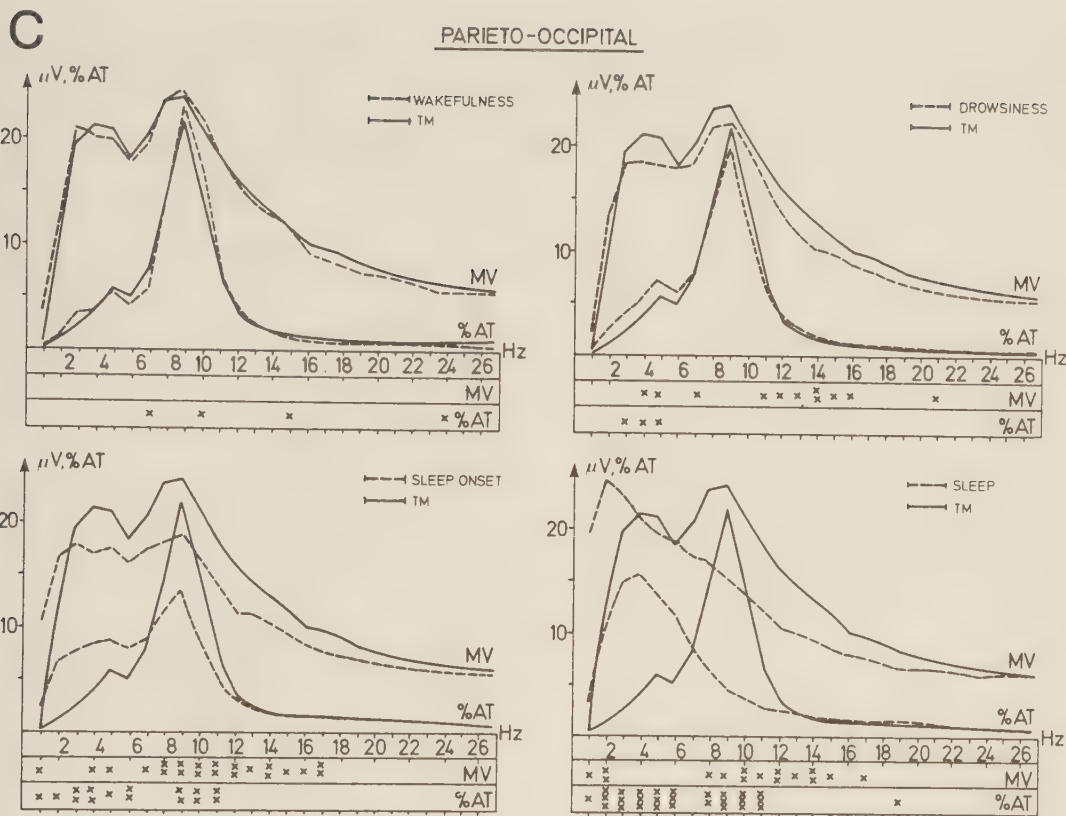


Fig. 1c. For legend see Fig. 1a.

TABLE II

Fronto-central, temporal and parieto-occipital EEG mean frequencies (mean $\pm$ S.E.M.) measured 5, 10 and 15 min (TM₅, TM₁₀ and TM₁₅) after meditation start. Significant differences are indicated by the statistical probability level (Wilcoxon Matched-Pairs Signed-Ranks test).

EEG derivation	TM ₅ ($\bar{x} \pm$ S.E.M.)	Difference TM ₅ —TM ₁₀	TM ₁₀ ($\bar{x} \pm$ S.E.M.)	Difference TM ₁₀ —TM ₁₅	TM ₁₅ ($\bar{x} \pm$ S.E.M.)	Difference TM ₅ —TM ₁₅
F3-C3	10.3 $\pm$ 0.40	n.s.	10.3 $\pm$ 0.47	n.s.	9.9 $\pm$ 0.39	$P < 0.05$
F4-C4	9.8 $\pm$ 0.49	n.s.	9.6 $\pm$ 0.41	n.s.	9.5 $\pm$ 0.33	n.s.
T3-T5	10.5 $\pm$ 0.49	$P < 0.05$	10.1 $\pm$ 0.39	n.s.	9.9 $\pm$ 0.44	$P < 0.05$
P3-O1	10.2 $\pm$ 0.27	n.s.	10.0 $\pm$ 0.34	n.s.	10.4 $\pm$ 0.42	n.s.
P4-O2	10.3 $\pm$ 0.27	n.s.	10.0 $\pm$ 0.27	n.s.	10.0 $\pm$ 0.24	n.s.
Total	10.2 $\pm$ 0.12	$P < 0.05$	10.0 $\pm$ 0.11	n.s.	9.9 $\pm$ 0.14	n.s.

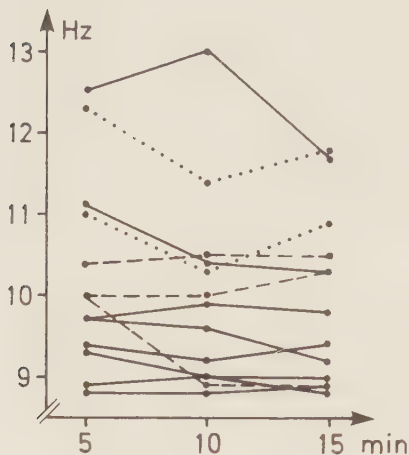


Fig. 2. The mean frequencies (average of all 5 regions) measured 5, 10 and 15 min after TM start. The solid lines represent the 8 subjects with a successful meditation, the stippled and dotted lines the 5 subjects with an unsuccessful. The dotted lines represent the 2 subjects who felt drowsy during meditation.

frequency and the number of years the meditators had practised TM ($r = 0.09$, $P > 0.1$).

Visual evaluation of the EEGs

All EEGs were evaluated as normal by visual inspection. During TM there were no theta bursts which met the criteria of Hebert and Lehmann (1977), i.e., a frequency between 4 and 7.5 c/sec, a minimum amplitude of 100 μ V and a minimum duration of 1 sec. Short trains of theta activity were, however, seen in a few of the subjects, but the amplitude of the theta activity was within the range of the background activity, and the duration never reached 1 sec.

Subjective experience of the meditation

Two out of 13 meditators stated that they had felt drowsy in periods during meditation. Eight meditators considered their meditation 'normal' or even better than normal, and the remaining 5, including the two who felt drowsy, thought their meditation was not as successful as usual. One felt tense because of

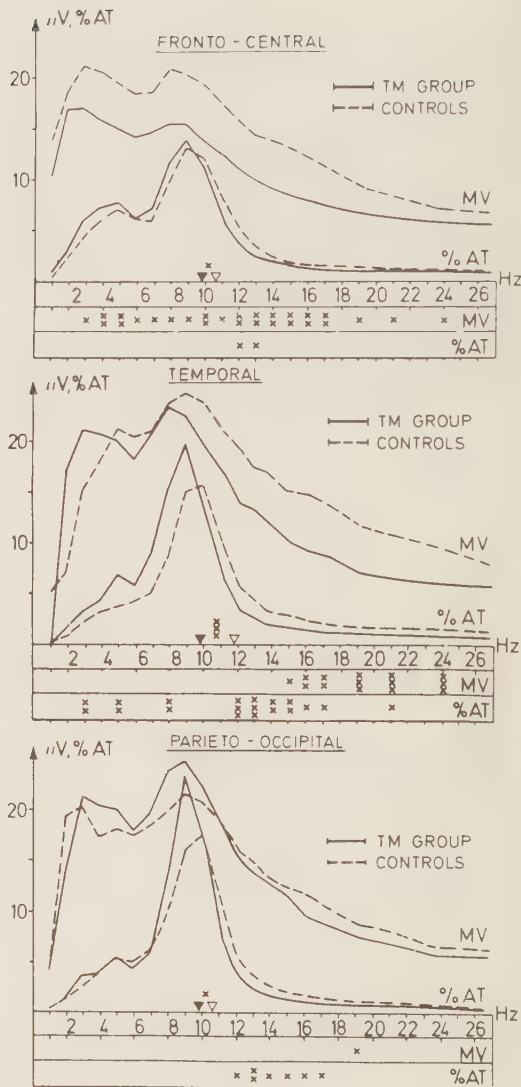


Fig. 3. The mean activity distributions (% AT) and the voltage distributions (MV) in EEGs from the fronto-central, temporal and parieto-occipital regions of the TM group (solid curves) and the control group (stippled curves). The mean frequency of the TM group ($\blacktriangledown$) and of the control group ($\triangledown$) are indicated. Significant differences between the TM and the control group are indicated at the corresponding frequency bands as well as at the mean frequencies on the abscissa (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; Mann-Whitney U test).

the needle electrodes, but fell asleep during the control session.

There were no consistent EEG patterns associated with a meditation considered as successful or unsuccessful. The EEGs of the two meditators who felt drowsy during meditation did not differ from the rest (Fig. 2).

Discussion

The term 'transcendental' meditation' (TM) was applied in this context to a short period (20 min) of meditation by the use of a meaningless mantra, with the aim of describing the concomitant EEG changes. It has nothing to do with the term 'transcendental meditation' used by the 'International Association for the Advancement of the Science of Creative Intelligence' and its affiliated organizations, to which this study has no adherence.

Quantitative analysis of the EEG during TM and during wakefulness, drowsiness, and sleep showed that experienced meditators are at a quantitative level of consciousness between wakefulness and drowsiness during meditation. During the 20 min of meditation there was an extraordinary stability of the EEG mean frequency in all meditators. This implies that these meditators were able, regardless of the examination situation, to put themselves into a state which electroencephalographically is characterized as a state between wakefulness and drowsiness. Further, they were able to maintain this state virtually unchanged during the 20 min of meditation, a phenomenon quite different from their normal pattern of relaxation. Most meditators thus fell asleep within 20 min of relaxation and all had considerable fluctuations in their state of consciousness during the control session. Although it should be remembered that meditation was performed in the sitting position and the control session in the supine, the difference is, however, striking.

Our findings are at variance with those of Tebécis (1975) who found no differences in EEG frequency between TM periods and non-

TM periods. Tebécis' material comprised a rather heterogeneous and inexperienced group, which might explain why a group analysis did not show any consistent changes. A comparative study between inexperienced and experienced meditators would be desirable.

In contrast to our findings, Wallace (1970), Banquet (1973) and Morse et al. (1977) reported that alpha activity during meditation was more regular and had a larger amplitude, indicating that the EEG during meditation is clearly different from the EEG during non-TM periods and not at all similar to the EEG during light drowsiness. In addition, Banquet reported development of a sustained beta activity of increased amplitude in 4 out of 12 subjects, which he ascribed to the state of transcendence. We have no explanation for these discrepancies. It should, however, be mentioned that 4 out of the 15 subjects in Wallace's material showed a different EEG pattern during TM. This pattern resembled the findings in the present study as well as findings described during zen meditation by Kasamatsu and Hirai (1966). The beta activity seen by Banquet and also mentioned by Morse et al. could be a quite unspecific phenomenon, as increased beta activity, especially if prominent frontally, is normally seen in some people during drowsiness and sleep onset (Kooi et al. 1978).

Pagano et al. (1976) found that an appreciable part of meditation sessions was spent in sleep, as evaluated by the EEG, which in some cases was later admitted to by the meditators. No sleep episodes were registered during TM in this study. It is unlikely that the examination situation could be the reason for this, since all subjects reached the sleep onset stage during the control session. An examination during one TM session only does not, however, exclude the possibility that sleep may occur during TM in general.

Several authors (Levine et al. 1977; Orme-Johnson 1977; Westcott 1977) have described an increased coherence between the cerebral hemispheres during TM. This could not be

further examined in this study because of the type of EEG analysis used. However, we found no intra- or interhemispheric differences concerning the quantity of EEG activity and EEG voltage during the course of TM.

The EEG mean frequency of the meditating group before and after TM was slightly, but significantly, slower than that of the control group. This finding is in accordance with Tebécis (1975), who found increased theta density in a TM group as compared to a control group. This could either be a result of practising TM or a premeditational phenomenon. Tebécis suggested that the EEG changes that occurred during TM were gradual, occurring slowly during long-term practise. We were not able to support this suggestion as we found no correlation between EEG frequency and 2–8 years of practising TM.

The possible specificity of theta bursts which Hebert and Lehmann (1977) found in one-third of their experienced meditators, but not in a control group which also consisted of novice meditators, could not be supported by this study of experienced meditators, as we found no theta bursts which could fulfil the criteria set by Hebert and Lehmann.

It is difficult by scientific means to relate the short-term physiological changes seen during TM to the beneficial long-term psychological effects claimed by the meditators. However, when we compare the physiological state of TM with the stages of sleep, with their known importance for psychological well-being, we cannot exclude that 20 min of meditation twice a day is of some importance. Further research is certainly needed before the objective value of meditation can be settled.

Summary

The EEGs of 13 experienced practitioners of transcendental meditation (TM) were recorded for 5 min preceding TM, during 20 min of TM and until 5 min after, as well as during closed-eyed wakefulness, drowsiness,

sleep onset and sleep. Thirteen healthy volunteers matched for age served as control subjects. Computer period-amplitude analysis of F3-C3, T3-T5, P3-O1, F4-C4 and P4-O2 epochs of 50–100 sec duration resulted in a frequency and amplitude spectrum (0.5–28.6 c/sec), and the mean frequency and the mean voltage of each EEG lead.

The EEG frequency spectra constituted a continuum with increasing theta and delta activity and decreasing alpha activity as the participants tended to fall asleep. The frequency spectrum during TM corresponded to a spectrum situated between that of wakefulness and drowsiness and remained virtually unchanged during the 20 min of meditation. The EEG mean frequency of the TM group was about 1 c/sec slower than that of the control group.

Intra- or interhemispheric differences between quantities of EEG activity remained stable during TM, nor did we observe any theta bursts.

There was no consistent EEG pattern associated with a successful or unsuccessful meditation, nor did the EEGs of two meditators who stated they had felt drowsy during TM show a different pattern.

Résumé

Résultats EEG obtenus durant la méditation mantra (méditation transcendentale). Etude quantitative, effectuée sous contrôle, chez des adeptes entraînés

Les EEG de 13 adeptes entraînés à la méditation transcendentale (MT) furent enregistrés pendant les 5 min précédant la MT, pendant 20 min de MT et les 5 min qui l'ont suivie, ainsi que durant la veille, yeux fermés, durant l'installation du sommeil et le sommeil. Treize volontaires en bonne santé, d'âges identiques, servirent de témoins. L'analyse sur calculeur des fréquences et amplitudes de F3-C3, T3-T5, P3-O1, F4-C4 et P4-O2 a permis d'établir des spectres d'amplitude et de

fréquence (0,5–28,6 c/sec), une fréquence moyenne et un voltage moyen pour chaque plot EEG.

Les spectres de fréquence EEG constituaient un continuum avec augmentation de l'activité delta et thêta et décroissance de l'activité alpha tandis que les sujets tendaient à s'endormir. Le spectre de fréquence durant la MT correspondait à un spectre intermédiaire entre celui de la veille et celui de l'assoupissement et restait pratiquement inchangé durant les 20 min de méditation. La fréquence moyenne EEG pour le groupe MT était d'environ 1 c/sec plus basse que celle du groupe témoin.

Les différences intra- ou interhémisphériques entre les quantités des activités EEG restèrent stables pendant la MT et nous n'avons pas non plus observé de bouffées thêta.

Il n'y avait pas de configurations EEG typiques associées à une méditation soit réussie soit manquée; pour 2 sujets qui firent état d'un assoupissement lors de la MT, les configurations ne furent pas non plus différentes.

The computer work was performed at the Department for Data Processing in Medicine, Gentofte Hospital.

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